JMAJ
Japan Medical Association Journal
Vol.48, No.5 May 2005

Editorial

Original Articles

Review Article

Case Report

Special Article

Current Activities of JMA

Medical News from Japan

Clinical Practice Guidelines of Japan: From Implementation to Evaluation

Naohito Yamaguchi*1

Clinical practice guidelines are systematically prepared documents that assist in making appropriate judgments under specific clinical situations. In Japan, in response to a proposal made by the Health Technology Assessment Promotion Panel of the Ministry of Health and Welfare (Chair: Fumimaro Takaku) to facilitate the preparation of such guidelines, a full-scale nationwide research project to prepare clinical practice guidelines was implemented in 1999. The Ministry of Health, Labor and Welfare (MHLW), through its grant-in-aid for scientific research, has been supporting the development of guidelines for the diagnosis and treatment of 26 diseases, and complete guidelines are already available for some of them. Further, at least 100 clinical practice guidelines have been completed by various independent medical societies.

Thus, the development of clinical practice guidelines is well underway in Japan, and MHLW has begun to lay additional stress on its project to promulgate guidelines. A judicial foundation, the Japan Council for Quality Health Care, is in charge of the project. This foundation was assigned in 2002 to provide medical information services under the support of an MHLW grant-in-aid for scientific research, and this service became available to the public in May 2004. Currently, guidelines for the diagnosis and treatment of 9 diseases, diabetes mellitus, subarachnoid hemorrhage, cerebral infarction, bronchial asthma, acute myocardial infarction, gastric ulcer, lung cancer, acute pancreatitis, and intracerebral hemorrhage, as well as relevant information, are available at http://minds.jcqhc.or.jp/. More than 7,000 individuals have registered to member users, pointing to the rapid spread of the guidelines in Japan.

An all-out effort is being made toward the further development of clinical practice guidelines, which will lead to the availability of more guidelines on the Internet. An important issue to be addressed is the extent to which the promulgation of clinical practice guidelines can actually contribute to the improvement of the quality of medical care. For clinical practice guidelines to fulfill their role, it will be necessary, for the first place, for a clinical practice guideline to be noticed of its existence by clinicians. Second, it will be important for it to be appreciated as to its usefulness. The ultimate goal of clinical practice guidelines is to achieve favorable changes in daily practices and, eventually, substantial improvement in the outcome of treatment. Thus, it is important to evaluate the influence of the guidelines on actual medical care. In this regard, an article in the current issue, "Clinical effectiveness of evidence-based guidelines for pain management of terminal cancer patients in Japan," by Fukui et al., is deserving of attention. This study compared, using an epidemiologic technique, the outcomes of actual treatments given to patients as well as the changes in pain care practices before and after the publication of related clinical practice guidelines. This study is also valuable in that it provides a model for the evaluation of clinical practice guidelines that should be implemented in the future.

Although Japan's attempt to achieve better medical care through clinical practice guidelines is in the early stage, gradual but steady progress can be expected as the various challenges are overcome. To this end, it will be necessary for clinicians to respond to these guidelines with an attitude of careful evaluation.

*1 Department of Hygiene and Public Health (II), Tokyo Women's Medical University, Tokyo
Correspondence to: Naohito Yamaguchi MD, Dr Med Sci, Professor, Department of Hygiene and Public Health (II), Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. Tel: 81-3-3353-8111, Fax: 81-3-5269-7420, E-mail: yamaguch@research.twmu.ac.jp

Original Article

Clinical Effectiveness of Evidence-based Guidelines for Pain Management of Terminal Cancer Patients in Japan

JMAJ 48(5): 216–223, 2005

Tsuguya Fukui,[*1] Osamu Takahashi,[*2] Mahbubur Rahman,[*3] Keiko Iino,[*4] Yosuke Uchitomi,[*5] Setsuro Ogawa,[*6] Midori Kita,[*7] Izo Kimijima,[*8] Hitoshi Kondo,[*9] Michihiro Shino,[*10] Yoko Takumi,[*11] Akira Tsuneto,[*12] Keiko Hamaguchi,[*13] Maki Matsumoto,[*14] Taketo Mukaiyama,[*15] Makoto Yamamuro,[*16] Akihiko Watanabe,[*17] Osamu Setoyama,[*18] Kazuaki Hiraga[*19]

Abstract

Background The Japanese Society for Palliative Medicine (JSPM) set guidelines for cancer pain management in 1999. However, the clinical effectiveness of the guidelines has not yet been examined.

Methods Two groups of consecutive patients with cancer admitted to 37 national hospitals (collaborating hospitals for pain management research in Japan) were recruited, one from August to September 1999 (who received the standard treatment in use before the distribution of JSPM guidelines) and the other from July 2000 to May 2001 (who received treatment after the distribution of JSPM guidelines). Demographics, type of cancer and other baseline information were recorded for both groups. In addition, the intensity of pain (evaluated on a 4-level scale of none, mild, moderate, severe; and a visual analog scale of 0 to 100), its duration, source and location were recorded at base line, 1 week and 2 weeks after the start of pain management for two groups and compared by statistical methods.

Results A total of 314 cancer patients received the standard pre-guidelines treatment from August to September 1999 and 106 patients received the post-guidelines treatment from July 2000 to May 2001. No significant differences have been observed between the two groups in terms of baseline characteristics. There were more patients with lung cancer in the pre-guidelines treatment group and more with gastric cancer in the post-guidelines treatment group. More oral opioids ($P = 0.004$) and more adjuvant drugs such as nonsteroidal anti-inflammatory drugs ($P = 0.001$) and hydroxyzine ($P = 0.001$) were used in the post-guidelines treatment group than in the pre-guidelines treatment group and the opposite was true for intravenous ($P = 0.022$) and suppository ($P = 0.041$) opioids. More patients in the post-guidelines treatment group became pain free after 2 weeks compared to those in the pre-guidelines treatment group (14.7% vs. 8.8%) ($P = 0.036$). Moreover, significantly fewer adverse reactions and more recovery from the adverse reactions which did occur were found in the post-

*1 St. Luke's International Hospital, Tokyo, *2 Department of General Medicine and Clinical Epidemiology, Kyoto University Graduate School of Medicine, Kyoto, *3 St. Luke's Life Science Institute, Tokyo, *4 National College of Nursing, Kiyose, Tokyo, *5 Psycho-Oncology Division, National Cancer Center Research Institute East, Chiba, *6 Department of Anesthesiology, Nihon University School of Medicine, Tokyo, *7 Department of Radiology, Fuchu Hospital, Tokyo,*8 Minami Clinic, Yasuhara General Hospital, Fukushima, *9 Center of Gastroenterology, Tonan Hospital, Sapporo, *10 Department of Pharmacy, Shizuoka Cancer Center, Nagaizumi, *11 Grey Nuns Community Hospital, Edmonton, Canada, *12 Department of Clinical Thanatology, Osaka University Graduate School of Human Sciences, Osaka, *13 Department of Nursing, The Cancer Institute Hospital of JFCR, Tokyo, *14 Department of Anesthesiology, Sapporo Medical University, Sapporo, *15 Department of Medicine, The Cancer Institute Hospital of JFCR, Tokyo, *16 Department of Anesthesiology and Emergency Medicine, Tohoku University Postgraduate Medical School, Sendai, *17 Department of Anesthesiology, Higashi Sapporo Hospital, Sapporo, *18 Clinical Science Institute, Natori, *19 Surgical Operation Division, National Cancer Center Hospital, Tokyo
Correspondence to: Tsuguya Fukui MD, MPH, PhD, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan. Tel: 81-3-3541-5151, Fax: 81-3-3544-0774, E-mail: fkts@luke.or.jp

guidelines treatment group than in the pre-guidelines treatment group.

Conclusion The implementation of JSPM pain management guidelines for cancer patients was effective in increasing the proportion of patients relieved of pain and in reducing adverse reactions to opioids.

Key words Pain management, Japanese Society for Palliative Medicine, Treatment guidelines, Cancer pain, Opioids and non-opioid analgesics, Clinical effectiveness

Introduction

The main goal of palliative care of patients with incurable cancer is to improve their quality of life by managing pain and other symptoms. It has been reported that 70% of all cancer patients suffer from pain[1] and that 36% of those with metastasis have pain severe enough to impair their physical and social functioning.[2] Opioids, the most effective medicine for suppressing pain, often cause adverse reactions such as constipation, nausea/vomiting and drowsiness. This fact raises fear in many cancer patients,[3–5] hindering the adequate use of pain medications including opioids and non-opioid analgesics.[6]

For this reason, the World Health Organization (WHO) developed clinical guidelines for pain and symptom management as a part of palliative care in 1986.[7] The guidelines consist of a three-step "analgesic ladder" approach that was reportedly effective in relieving pain in 69–100% of cancer patients.[8]

However, patient outcomes have not always been consistent and satisfactory. Case series studies, for example, showed that 45–65% of patients with cancer suffered intractable pain[9,10] and over 70% reported at least one symptom during the course of treatment[11] despite the employment of recommended analgesic regimens. Moreover, the validity of studies to assess the effectiveness of WHO guidelines was questioned due to methodological limitation, in particular, the lack of controls for comparison.[8]

In Japan, the Japanese language version of the WHO guidelines has been available since 1987. Although the proportions of complete pain relief among cancer patients in Japan rose from 38% in 1986 to 57% in 1998,[12,13] cancer pain management remains a critical issue in palliative care. To further improve the control of cancer pain, the Japanese Society for Palliative Medicine (JSPM) established guidelines in 1999 based on the best available evidence from scientific studies in and outside of Japan.[14]

We conducted this study to explore the effectiveness of the JSPM guidelines in terms of pain relief, adverse reactions, and quality of life in cancer patients.

Methods

The guidelines

The Evidence-based Cancer Pain Management Guidelines were developed in 1999 by the Guidelines Preparation Committee of the JSPM as described elsewhere.[15] They were formulated in such a manner that the recommended type and dosage of drugs were adapted to local settings in Japan. These JSPM guidelines were distributed in October 1999 to 37 national hospitals throughout the country.

Design and patients

Directors at 37 national hospitals in Japan were invited to participate in this study. These hospitals had already been collaborating in a series of surveys on pain management for cancer patients since 1986. Two groups of consecutive patients with terminal cancer admitted to these hospitals were recruited, one from August to September

1999 (pre-guidelines treatment group) and the other from July 2000 to May 2001 (post-guidelines treatment group). The patients of the pre-guidelines treatment group received pain management before the distribution of the JSPM guidelines and those of the post-guidelines treatment group did so after the distribution of the JSPM guidelines. All patients gave informed consent in writing before participating in this study. Changes in the type and dosage of analgesics, and the management of adverse reactions, if any, were recorded by the physicians in charge of subject patients.

Measurements

At baseline, information on demographics and type of cancer was recorded from medical records. A battery of pain measurement tests were conducted at baseline, 1 week and 2 weeks after the start of pain management by either the pre-guidelines treatment or the post-guidelines treatment. The primary outcome index was the degree of subjective pain in terms of duration and intensity. Intensity was measured by a 4-level scale (none, mild, moderate, or severe) and visual analog scale (VAS) on a 0-to-100 range, with 0 representing no pain and 100 worst pain. The duration was measured as the proportion of the day in which the average and the worst pain were experienced. The source and location of pain were also recorded by attending physicians. The secondary outcomes indices were analgesic dosing and adverse reactions of the analgesics. These data were extracted from medical records.

Statistical analysis

SAS was used for all statistical analyses. Outcome and baseline values for the pre-guidelines treatment group and the post-guidelines treatment group were compared by means of t-tests for continuous variables and of chi-square tests for categorical variables. T-tests were also used to compare changes in scores from the baseline to one week and two weeks for the two groups.

The calculation of sample size was based on a two-tailed t test with a significance level of 0.05, a power level of 0.80, and a clinical effect size of 10 VAS score of average pain reduction and a standard deviation of 25 VAS score from baseline to 2 weeks between the two treatment groups. The required sample size was calculated to be 99 for each group.

Results

Patient characteristics

A total of 420 cancer patients were enrolled in the study; 314 patients received the pre-guidelines treatment from August to September 1999 and 106 patients received the post-guidelines treatment from July 2000 to May 2001. Patient characteristics are shown in Table 1. The mean age was 63 years (range: 7 to 96 years) with men representing 58% of all patients. Underlying diseases were lung cancer (22.3%), colorectal cancer (15.9%), and gastric cancer (10.8%). Patients had an average of two pain locations, a VAS score of 29.8 for the average pain, and a VAS score of 54.0 for the worst pain.

Between the two groups, there were no significant differences in age, sex, baseline VAS for the average pain, baseline VAS for the worst pain, baseline duration of pain, performance status and the ability to ingest orally. However, significant differences were found in the diagnosis and the type of previous treatment aimed at curing the cancer. The number of patients with gastric cancer was significantly greater in the pre-guidelines treatment group than in the post-guidelines treatment group while the number of patients with lung cancer and the proportion of patients who received radiation therapy were significantly greater in the post-guidelines treatment group than in the pre-guidelines treatment group.

Pain assessment

The changes in VAS score for the average and worst pain, duration of the average pain

Table 1 Baseline patient characteristics

	Pre-guidelines treatment group (n=314)	Post-guidelines treatment group (n=106)	Both groups (n=420)	P value
Age, years (SD)	62.6 (12.8)	63.7 (11.6)	62.9 (12.5)	0.20
Sex, %				
Male	57.9	57.7	57.8	1.0
Diagnosis, %				
Lung cancer	19	32.7	22.3	$<0.01^{\dagger}$
Colorectal cancer	17.1	12.1	15.9	0.2
Gastric cancer	12.2	6.5	10.8	$<0.01^{\dagger}$
Breast cancer	9.1	9.3	9.2	1.0
Pancreatic cancer	7.0	5.6	6.7	0.67
Hepatocellular carcinoma	6.1	4.7	5.8	0.58
Others	29.5	29.1	29.3	0.99
Metastasis	86.5	86.4		0.94
Type of treatment				
Operation, %	5.2	1.9	4.4	0.15
Chemotherapy, %	28.1	24.5	27.2	0.48
Radiation, %	24.7	35.8	27.4	$0.03^{\dagger}$
Palliative Care, %	43.6	42.5	43.3	0.83
PS, %				0.89
0–2	51.3	52.0	51.3	
3–4	48.7	48.0	48.7	
Oral ingestion				
Possible, %	80.7	86.5	82.1	0.18

Note: † = $P<0.05$; PS = performance status

Table 2 Pain assessment

	Pre-guidelines treatment group	Post-guidelines treatment group	P value
Duration of pain (SD), hr			
Mean at baseline	6.65 (7.27)	8.63 (8.35)	0.08
1 week after	5.17* (6.23)	5.75* (6.53)	0.56
2 weeks after	4.29* (5.25)	5.54* (6.42)	0.07
0 day–14 days	2.17 (6.21)	2.56 (6.57)	0.64
VAS at usual (SD), mm			
Mean at baseline	29.1 (24.8)	32.1 (24.8)	1.00
1 week after	25.2* (23.5)	27.2* (25.1)	0.43
2 weeks after	22.8* (22.9)	23.5* (23.6)	0.78
0 day–14 days	6.7 (25.6)	9.8 (26.8)	0.33
VAS at worst (SD), mm			
Mean at baseline	55.1 (31.3)	51.0 (30.3)	0.73
1 week after	45.1* (30.6)	42.4* (29.8)	0.77
2 weeks after	39.2* (31.1)	36.2* (29.2)	0.49
0 day–14 days	15.5 (30.6)	15.3 (27.1)	0.94
Duration of sleep (SD), hr			
Mean at baseline	8.05 (5.87)	7.28 (2.56)	0.00
1 week after	7.95 (3.44)	7.92* (2.56)	0.00
2 weeks after	8.17* (4.33)	8.32* (3.53)	0.03
14 days–0 day	0.47 (2.59)	1.05 (3.29)	0.09

*: Statistical comparison was performed between baseline and follow-up points using paired t-test: * = $P<0.05$

Note: 0 day = baseline; 7 days = midpoint; 14 days = endpoint

Mean value baseline minus mean value after 14 days do not correspond exactly to the value in the 0 day–14 days row due to missing data.

Table 3 Prescriptions by physicians

Drug, %	Pre-guidelines treatment group	Post-guidelines treatment group	Both groups	P value
Opioids				
Morphine	71.0	68.9	70.5	0.67
Morphine (p.o.)	12.8	24.5	15.7	<0.01†
Morphine (i.v.)	15.3	6.6	13.2	0.02†
Morphine sulfate (p.o.)	38.7	37.7	38.5	0.86
Morphine (supp.)	12.8	5.7	11.1	0.04†
Pentazocine (p.o.)	8.5	1.9	6.9	0.02†
Pentazocine (i.v.)	1.2	0	0.9	0.25
Buprenorphine (supp.)	1.2	1.9	1.4	0.26
Buprenorphine (i.v)	1.2	0	0.9	0.25
Non-steroidal anti-inflammatory drugs	30.5	50.0	35.2	<0.01†
Diclofenac (supp.)	12.5	23.6	15.2	<0.01†
Loxoprofen (p.o.)	11.9	19.8	13.8	0.04†
Diclofenac (p.o.)	4.9	0.9	3.9	0.07
Others				
Hydroxizine (p.o.)	0.3	4.7	1.4	<0.01†
Prednisolone (i.v.)	0.9	0	0.7	0.32
Imipramine	0.3	0.9	0.5	0.4
Metoclopramide (p.o.)	0	1.9	0.4	0.01†

Note: † = P<0.05; supp. = suppository; p.o. = per os; i.v. = intravenous

and duration of sleep from baseline to 2 weeks were 6.7 VAS score, 15.5 VAS score, 2.17 hr and 0.47 hr in the pre-guidelines treatment group, and 9.8 VAS score, 15.3 VAS score, 2.56 hr and 1.05 hr in the post-guidelines treatment group, respectively, (Table 2) with no significant difference between the two groups. However, both groups showed a steady downward trend during the study period. Patients who allegedly had no pain at baseline due to ongoing therapy accounted for 10.8% in the pre-guidelines treatment group and 11.4% in the post-guidelines treatment group. The proportion of patients free from pain at 2 weeks was 19.6% in the pre-guidelines treatment group and 26.1% in the post-guidelines treatment group. Thus, the proportion of patients who were relieved of pain during the study period was higher in the post-guidelines treatment group compared to that in the pre-guidelines treatment group (14.7% vs. 8.8%, P = 0.036).

Analgesic use

Analgesics used in the study periods are shown in Table 3. Although the total use of morphine did not significantly differ between the two groups, significantly more oral opioids were used in the post-guidelines treatment group than in the pre-guidelines treatment group (P = 0.004) and the opposite was true for intravenous (P = 0.022) and suppository (P = 0.041) opioids. Moreover, significantly more adjuvant drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) (P = 0.001) and hydroxizine (P = 0.001) were used in patients in the post-guidelines treatment group than the pre-guidelines treatment group. The use of tricyclic antidepressants and prednisolone did not significantly differ between the two groups.

Management of adverse reactions

Symptoms of adverse reactions are shown in Table 4. The major adverse reactions to opioids at baseline included constipation (53.3% in the pre-guidelines treatment group; 32.7% in the post-guidelines treatment group), nausea/vomiting (23.2%; 15.4%), and drowsiness (38.7%; 29.8%).

Table 4 Adverse reactions

Adverse reactions	Pre-guidelines treatment group	Post-guidelines treatment group	Both groups	P value
Constipation at baseline, %	53.3	32.7	48.2	<0.01†
Incidence, %	23.1	11.8	19.4	0.05
Cured patients, %	6.4	17.3	9.1	0.02†
Vomiting at baseline, %	23.2	15.4	21.2	0.09
Incidence, %	14.9	5.7	12.4	0.03†
Cured patients	13.2	40.6	20.3	0.01†
Drowsiness at baseline, %	38.7	29.8	36.4	0.11
Incidence, %	26.5	9.5	21.6	<0.01†
Cured patients, %	3.7	19.4	8.0	0.01†

Note: † = $P<0.05$

Significantly fewer adverse reactions occurred in the post-guidelines treatment group than in the pre-guidelines treatment group in terms of nausea/vomiting ($P=0.03$) and drowsiness ($P<0.01$). At the same time, the proportion of patients who recovered from such adverse reactions as constipation ($P=0.02$), nausea/vomiting ($P=0.01$), and drowsiness ($P=0.01$) were significantly greater in the guidelines treatment group than in the pre-guidelines treatment group.

Discussion

Our study showed that more patients in the post-guidelines treatment group became pain free after 2 weeks compared to those in the pre-guidelines treatment group. Moreover, significantly fewer adverse reactions and more recovery from adverse reaction were found in the post-guidelines treatment group than in the pre-guidelines treatment group. However, there was no significant difference in the intensity of the average and the worst pain between the two groups. Contrary to our findings, Du Pen et al. showed in a randomized controlled trial that cancer patients treated in accordance with pain management guidelines had a statistically shorter duration of the average pain, but not of the worst pain, than those treated without guidelines.[16] The lack of significant reduction in pain intensity in the current study could have several reasons. First, adjuvant drugs were not prescribed more frequently in the post-guidelines treatment group than the pre-guidelines treatment group in spite of the recommendation of the use of these drugs in the JSPM guidelines. For example, tricyclic antidepressant drugs are recommended as the first-line adjuvant therapy for neuropathic pain[17,18] and corticosteroids for acute nerve compression, visceral distention and increased intracranial pressure.[19] However, there were no significant differences in the rate of prescriptions of these adjuvant drugs between the two groups. This contrasts with the report by Du Pen et al, in which significantly more tricyclic antidepressants were used in the post-guidelines treatment group than in the pre-guidelines treatment group.[16] In addition to physicians' reluctance to prescribe opioids, which was already shown to be a barrier to adequate cancer pain management,[19,20] a similar reluctance to prescribe antidepressants is likely to be an important factor. Education and training of physicians on the adequate use of antidepressants is mandatory. Second, the observation period of this study was only 2 weeks, much shorter than that of the study by Du Pen et al. which was 3 months.[16]

The current study showed that oral opioids and NSAIDs were prescribed significantly more in the post-guidelines treatment group than in the pre-guidelines treatment group. Similar findings have been reported

from a case series study.[11] In the randomized controlled trial by Du Pen et al, significantly more NSAIDs were prescribed for the guidelines treatment group, although this tendency was not observed for opioids.[16] NSAIDs are generally prescribed for relieving pain of mild to moderate intensity and pain due to bone metastasis[21] and soft-tissue infiltration. This is because these drugs were shown to have not only a fast acting analgesic effect but also an opioid-sparing effect when used as adjuvant drugs.[22] The combination with opioids may well result in a reduction of the dosage of opioids leading to fewer side effects from opioids. For these reasons, a change in physicians' attitude towards increased use of NSAIDs in accordance with the JSPM guidelines should bring benefits to cancer patients.

The most common adverse reactions to the opioids among our patients were constipation, nausea/vomiting, and drowsiness, as reported in previous studies.[4] The proportion of patients who developed such adverse reactions was significantly smaller in the post-guidelines treatment group than in the pre-guidelines treatment group. The JSPM guidelines describe how to prevent adverse reactions to opioids by prescribing prophylactically laxatives and antiemetics from the start of pain management. In fact, several case series showed that adverse reactions to opioids were significantly reduced by following the WHO guidelines.[4,5,11] The current study has confirmed this effectiveness of clinical guidelines in reducing adverse reactions.

There are several limitations to the current study. The major concern is the non-randomized and non-parallel nature of the study design employed, which could result in a measurement bias, since physicians treating patients in the post-guidelines treatment group were not blinded to the use of the guidelines. Furthermore, there might have been a secular trend toward better pain management during the interval of approximately one year between the pre-guidelines treatment group and the post-guidelines treatment group. In addition, the VAS employed here may not be sensitive enough to reflect the complexity of the pain experience in individual patients. Finally, the number of patients (106) in the post-guidelines treatment group was unexpectedly smaller than that (314) in the pre-guidelines treatment group. In spite of these limitations, the current study provides important evidence of the clinical effectiveness of the evidence-based guidelines.

In conclusion, the implementation of JSPM guidelines was effective in increasing the proportion of terminal cancer patients relieved of pain and in reducing adverse reactions to opioids.

References

1. Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalized patients with advanced cancer. J Clin Oncol. 1992;10:149–155.
2. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med. 1994;330:592–596.
3. Levin DN, Cleeland CS, Dar R. Public attitudes toward cancer pain. Cancer. 1985;56:2337–2339.
4. Mercadante S. Pain treatment and outcomes for patients with advanced cancer who receive follow-up care at home. Cancer. 1999;85:1849–1858.
5. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995;63:65–76.
6. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 3. Clinical strategies to improve opioid responsiveness. J Pain Symptom Manage. 2001;21:338–354.
7. World Health Organization. Cancer pain relief. Geneva: World Health Organization; 1986.
8. Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. JAMA. 1995;274:1870–1873.
9. Banning A, Sjogren P, Henriksen H. Treatment outcome in a multidisciplinary cancer pain clinic. Pain. 1991;47:129–134; discussion 127–128.
10. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. Pain. 1990;41:273–281.
11. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain. 2001;93:247–257.
12. Hiraga K. The recent status of the management of cancer pain. Pain Clin. 1999;20:479–483.
13. Hiraga K, Mizuguchi T, Takeda F. The incidence of cancer pain and improvement of pain management in Japan. Postgrad Med J. 1991;67:S14–25.

14. The Japanese Society of Palliative Medicine. Evidence-based medicine-supported cancer pain management guidelines. 1999.
15. Hiraga K, Nozaki-Taguchi N. Usefulness of the evidence-based medicine-supported cancer pain management guidelines. Eur J Pain. 2001;5:103–108.
16. Du Pen SL, Du Pen AR, Polissar N, Hansberry J, Kraybill BM, Stillman M, Panke J, Everly R, Syrjala K. Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. J Clin Oncol. 1999;17:361–370.
17. Eija K, Tiina T, Pertti NJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain. 1996;64:293–302.
18. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain. 1996;68:217–227.
19. Watanabe S, Bruera E. Corticosteroids as adjuvant analgesics. J Pain Symptom Manage. 1994;9:442–445.
20. Larue F, Colleau SM, Fontaine A, Brasseur L. Oncologists and primary care physicians' attitudes toward pain control and morphine prescribing in France. Cancer. 1995;76:2375–2382.
21. Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. Ann Intern Med. 1993;119:121–126.
22. Lomen PL, Samal BA, Lamborn KR, Sattler LP, Crampton SL. Flurbiprofen for the treatment of bone pain in patients with metastatic breast cancer. Am J Med. 1986;80:83–87.
23. Mercadante S, Sapio M, Caligara M, Serretta R, Dardanoni G, Barresi L. Opioid-sparing effect of diclofenac in cancer pain. J Pain Symptom Manage. 1997;14:15–20.

The Brachial-Ankle Pulse Wave Velocity Is a Better Predictor for Pulse Pressure than Augmentation Index in Older Hypertensives

JMAJ 48(5): 224–233, 2005

Masanori Munakata,[*1] Tohru Nunokawa,[*2] Kaoru Yoshinaga,[*2] Takayoshi Toyota[*1]

Abstract

The brachial-ankle pulse wave velocity (PWV) is a new measure for arterial stiffness. The relative contribution of systemic arterial stiffness and wave reflection to the genesis of pulse pressure remains unclear. To address this issue, we measured blood pressure, heart rate, brachial-ankle PWV, and augmentation index (AI) of the left common carotid artery in young and older hypertensives before and after sublingual administration of nitroglycerin, using a new automatic device. Pulse pressure was larger and brachial-ankle PWV and AI were significantly higher in the older than in the younger group. Both brachial-ankle PWV and AI were significantly and positively correlated with pulse pressure in the older group. In multiple regression analysis, the brachial-ankle PWV was an independent contributor for pulse pressure, but AI was not. Nitroglycerin significantly lowered mean blood pressure in both groups but reduced pulse pressure only in the older group. Nitroglycerin similarly reduced AI in the two groups but reduced the brachial-ankle PWV by about 74% more in the older group. The change in pulse pressure after nitroglycerin was significantly correlated with that in brachial-ankle PWV ($r = 0.384$, $P < 0.00005$) but not with that in AI in the old group. Both heart rate and left ventricular ejection time were similar for either condition. These data suggest that increased systemic arterial stiffness, but not wave reflection, plays a prime role in the regulation of pulse pressure in older hypertensive patients. Expected reduction in pulse pressure after nitroglycerin is possibly offset by an aortic mechanism in young hypertensives.

Key words Pulse wave velocity, Augmentation index, Hypertension, Arteriosclerosis, Pulse pressure

Introduction

Pulse pressure, a marker of large artery stiffness, has recently emerged as an important predictor of cardiovascular morbidity and mortality.[1–3] Several studies conducted over the past few years have reported that increased pulse pressure is associated with more advanced target organ damage at the carotid, renal, and cardiac levels.[4–8] Thus, it is critically important to know underlying mechanisms of increased pulse pressure to adequately control this parameter.

Hemodynamic regulatory mechanisms involved in hypertension change with age.

*1 Preventive Medical Center, Tohoku Rosai Hospital, Sendai
*2 Division of Hypertension and Cardiology, Tohoku Rosai Hospital, Sendai
Correspondence to: Masanori Munakata MD, PhD, Preventive Medical Center, Tohoku Rosai Hospital, 3-21 Dainohara 4, Aoba-ku, Sendai, Miyagi 981-8563, Japan. Tel: 81-22-275-1111, Fax: 81-22-275-7541, E-mail: munakata.@tohokuh.rofuku.go.jp
A part of this study was presented in the 69th annual scientific meeting of the Japanese Circulation Society held in Yokohama on March 21, 2005.

In the young to middle generations, high blood pressure is maintained by high cardiac output and/or increased total peripheral resistance, and both systolic and diastolic hypertension occur. In the older generation, increased arterial stiffness further impairs Windkessel properties of large elastic arteries;[9] indeed, large arteries can instantaneously accommodate the volume of blood ejected from the heart, storing part of the stroke volume during systolic ejection and draining this volume during diastole, thereby ensuring continuous downstream perfusion. The loss of the cushioning function increases early systolic peak in response to a similar degree of ventricular ejection and decreases subsequent diastolic blood pressure, leading to an increase in pulse pressure.

In addition to these direct mechanisms, arterial stiffening also increases pulse pressure by indirect mechanisms. It is well known that systolic blood pressure is augmented by the reflection of pressure from the periphery of the circulation to the aortic root.[10] Increased pulse wave velocity (PWV) because of arterial stiffening results in earlier arrival of the reflected wave and thus, increased augmentation during early systole. This pressure augmentation in the proximal portion of the arterial system is determined not only by PWV but also by the intensity and timing of reflected pressure waves.[10] Although the left ventricular ejection time (LVET) is known to affect pulse pressure,[9] this parameter remains stable or even decreases with age. Thus, central factors that determine pulse pressure in the older generation are arterial stiffness and the impact of reflected wave from the periphery.

Relative contributions of arterial stiffness and wave reflection to the genesis of pulse pressure remain unclear. Moreover, those relationships should change with age. To address these issues, we compared blood pressures, brachial-ankle PWV (a new measure of systemic arterial stiffness), and augmentation index (AI) of the left common carotid artery (a measure of the impact of wave reflection in central artery) between young and old hypertensive patients. We studied the conditions at rest and after sublingual administration of nitroglycerin to examine the effect of vascular smooth muscle cell tone of the muscular artery or arteriole. Recent work has shown that nitroglycerin markedly reduces AI but has much less influence on aortic PWV.[11] The brachial-ankle PWV may be differently affected by nitroglycerin compared to carotid-femoral PWV because the brachial-ankle PWV includes not only aortic characteristics, but also lower limb artery characteristics. This study is the first to examine the effects of nitroglycerin administration on the brachial-ankle PWV.

Methods

Subjects

We studied 222 patients who exhibited clinic blood pressures ≧140 mmHg systolic or ≧90 mmHg diastolic on at least two visits. All participants received a standardized questionnaire concerning demographic data, past medical history, current medications, and personal habits, such as cigarette smoking. None of the subjects reported being under treatment for hypertension within at least the past month.

Blood was drawn in the morning after overnight fasting for at least 12 hr. Fasting blood sugar, total cholesterol, HDL-cholesterol, triglycerides, and plasma creatinine concentrations were measured by standard methods. Dyslipidemia was defined as a total cholesterol concentration ≧220 mg/dL, the use of a hypocholesterolemic drug, or triglyceride concentration ≧150 mg/dL. Diabetes mellitus was defined as a fasting blood glucose ≧126 mg/dL or the use of oral hypoglycemic agents. Patients with secondary hypertension, cancer, insulin-dependent diabetes, or renal insufficiency (plasma creatinine concentration >2.0 mg/dL) were not included in the study. Patients with peripheral arterial disease with an ankle pressure index below 0.9 were

excluded because precise measurement of the tibial arterial pressure wave was difficult in those patients. Finally, 200 patients with essential hypertension (age, 59.6 ± 1.6 years; range, 32 to 81) were included in the study.

Evaluation of hemodynamic parameters and arterial function

Blood pressure, heart rate, brachial-ankle PWV, and carotid augmentation index (AI) were studied using a new device, the AT-form PWV/ABI (Colin, Komaki, Japan). The details of the methodology and clinical application of this device have been described elsewhere.[12–14] In brief, the instrument simultaneously records right and left brachial and tibial arterial pressure wave forms, lead I of the electrocardiogram, and a phonocardiogram. A carotid tonometry sensor also was coupled with this device for analysis of the common carotid arterial wave. Occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were placed around both arms and ankles for pulse wave analysis and blood pressure measurements. The time difference between brachial and ankle arterial pressure wave (ΔT) was determined by the foot-to-foot method based on wave front velocity theory.[15] The distance between the arm and ankle (D) was calculated based on anthropometric data for the Japanese population. Finally, the brachial-ankle PWV was calculated as D/ΔT. The brachial-ankle PWV includes both aorta and lower limb artery characteristics and thus provides a more global arterial stiffness measure than traditional approaches do.[16]

The AI was examined by analysis of the left common carotid arterial wave (Fig. 1). The carotid arterial wave was analyzed using a multi-element tonometry sensor. The common carotid arterial wave was digitized at 1200 Hz. After identification of early and late systolic peaks (P and T, respectively) and the inflection point that separates them, we measured the height of the shoulder and the height above the shoulder (ΔP) of the late systolic peak attributable to the return of wave reflections from reflecting sites. The ratio of ΔP to the carotid pulse pressure (PP) defined the augmentation index (%), which estimated the effect of wave reflections in central arteries. The validity and reproducibility of the AI studied with this device has been reported previously.[17,18] Heart rate was calculated from the electrocardiogram. Left ventricular ejection time (LVET) was measured from the foot of the carotid arterial wave to the dicrotic notch.[19]

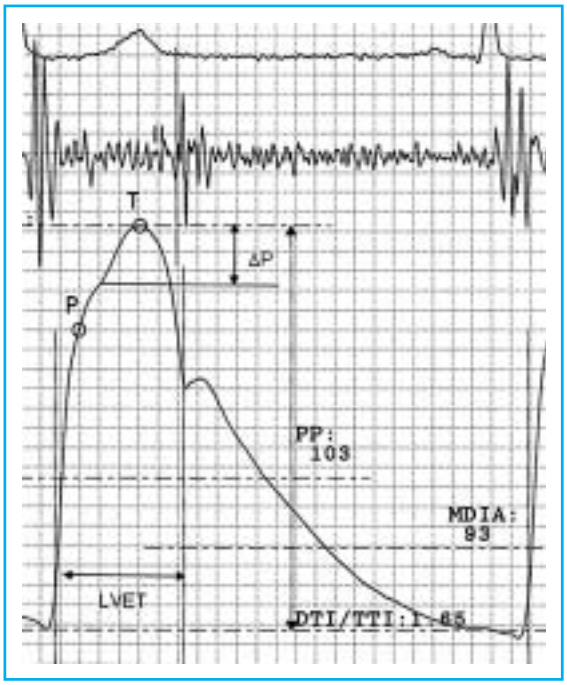


Fig. 1 Representative example of carotid pulse contour analysis in a 70-year-old hypertensive man. P and T indicate early systolic peak and late systolic peak, respectively. ΔP and PP denote the augmented systolic component by reflected wave and pulse pressure, respectively. LVET = left ventricular ejection time

All measurements were done at rest and after sublingual administration of nitroglycerin (0.3 mg, Myocor spray, Toaeiyo, Tokyo). Safety and tolerability of the nitroglycerin spray has been well confirmed.[20] It has been shown that blood pressures were lowered most 5 to 10 min after the sublingual administration of nitroglycerin spray;[20] thus, we repeated measurements 5 to 10 min after

Table 1 Clinical characteristics of the young and old groups

Variables	Young (n=91)	Old (n=109)	P value
Age (yrs)	46±9	70±7	<0.0000001
Sex (men,%)	45.9	49.5	n.s.
Height (cm)	162±9	156±8	<0.000005
Current smoker (%)	32%	24%	n.s.
Diabetes	9.9%	16.5%	n.s.
Dyslipidemia	61%	39%	0.05
Previous cardiovascular events	2.2%	16.5%	<0.005
Body mass index (kg/m^2)	24.5±3.7	23.6±3.1	n.s.
Systolic blood pressure (mmHg)	148±17	149±19	n.s.
Mean blood pressure (mmHg)	115±14	114±14	n.s.
Diastolic blood pressure (mmHg)	94±11	88±11	<0.001
Pulse pressure (mmHg)	54±10	61±13	<0.0005
Heart rate (bpm)	69±10	68±11	n.s.
Total cholesterol (mg/dL)	202±33	207±37	n.s.
HDL (mg/dL)	60.9±15.6	60.6±15.9	n.s.
Triglyceride (mg/dL)	149±133	102±59	n.s.
Fasting blood glucose (mg/dL)	102±18	107±25	n.s.
Cr (mg/dL)	0.64±0.14	0.66±0.16	n.s.
baPWV (cm/sec)	1,486±247	1,827±318	<0.0000001
AI (%)	16.7±15.5	22.6±14.1	<0.01
LVET (msec)	280±21	285±30	n.s.

baPWV = brachial-ankle pulse wave velocity; AI = augmentation index; LVET = left ventricular ejection time

nitroglycerin administration.

This study was approved by the Ethics Committee of Tohoku Rosai Hospital. The purpose of this study was fully explained, and all patients gave written informed consent.

Statistical analysis

All data are expressed as mean±standard deviation (SD). Subjects were classified as young (<60 yrs) and old (≧60 yrs) group. Correlation coefficients were calculated by Pearson's product-moment or Spearman's rank-order procedures when appropriate. Multiple regression analysis was used to assess independent associations between one dependent and two or more independent variables. Unpaired t-test was used for group comparison, and paired t-test was used to test for differences in variables after nitroglycerin. A P value less than 0.05 was considered to indicate significance. All analyses were performed using commercially available software (Stat Flex version 5.0 for Windows, Artec, Osaka, Japan).

Results

Table 1 shows the clinical characteristics of the young and old hypertensive groups. Previous cardiovascular events were more frequent in the old group (P<0.005). Diastolic blood pressure was lower in the old than in the young group (P<0.001), although systolic blood pressure did not differ. Consequently, pulse pressure was significantly greater in the old group (P<0.0005). Both brachial-ankle PWV and carotid AI were significantly greater in the old group compared to the young (P<0.0000001 and <0.01, respectively). Neither heart rate nor LVET differed between the two groups.

The brachial-ankle PWV was significantly correlated with pulse pressure as well as systolic, mean, and diastolic blood pressures in both young and old groups (Table 2). The AI was significantly and positively corre-

Table 2 Correlation coefficients between cardiovascular parameters and brachial-ankle PWV or carotid AI in young and old hypertensive patients

	Young				Old			
	baPWV		AI		baPWV		AI	
	r	P	r	P	r	P	r	P
SBP	0.522	<0.000001	0.402	<0.0001	0.529	<0.000001	0.184	n.s.
DBP	0.442	<0.00005	0.325	<0.005	0.341	<0.0005	0.06	n.s.
MBP	0.564	<0.000001	0.472	<0.000005	0.463	<0.000005	0.213	<0.05
PP	0.386	<0.0005	0.315	<0.005	0.460	<0.000005	0.203	<0.05
HR	0.220	<0.05	−0.276	<0.01	0.376	<0.0001	−0.418	<0.000005

baPWV = brachial-ankle pulse wave velocity; AI = augmentation index; SBP = systolic blood pressure; MBP = mean blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; HR = heart rate

Table 3 Hemodynamic responses to sublingual administration of nitroglycerin

Variables	Young (n = 91)	Old (n = 109)	P value
Δ systolic blood pressure (mmHg)	−10.2 ± 7.6*	−19.6 ± 11.7*	<0.000001
Δ mean blood pressure (mmHg)	−9.9 ± 6.9*	−15.4 ± 9.3*	<0.00001
Δ diastolic blood pressure (mmHg)	−10.9 ± 5.7*	−10.0 ± 7.4*	n.s.
Δ pulse pressure (mmHg)	0.7 ± 7.3	−10.1 ± 10.5*	<0.000001
Δ heart rate (bpm)	6.4 ± 4.6*	5.9 ± 4.9*	n.s.
Δ baPWV (cm/sec)	−165 ± 111*	−287 ± 163*	<0.000001
Δ AI (%)	−25.7 ± 13.6*	−28.4 ± 13.3*	n.s.
Δ LVET(msec)	−28 ± 12*	−32 ± 17*	n.s.

Δ means the value after nitroglycerin minus baseline value; baPWV = brachial-ankle pulse wave velocity; AI = augmentation index; LVET = left ventricular ejection time; *P<0.000001 vs. baseline value

lated with pulse pressure as well as other blood pressure parameters in the young group, but it was correlated only with mean blood pressure and pulse pressure in the older group. Heart rate was correlated positively with brachial-ankle PWV and negatively with AI in both groups. Multiple regression analysis was performed with pulse pressure as the dependent variable and mean blood pressure, brachial-ankle PWV, and AI as independent variables. In the older group, the mean blood pressure (P = 0.00001) and the brachial-ankle PWV (P = 0.007) were independent contributors to the pulse pressure, but AI was not. In the young group only, mean blood pressure (P = 0.0001) was an independent contributor for pulse pressure.

After sublingual administration of nitroglycerin, systolic, mean, and diastolic blood pressures were significantly lowered compared with baseline values in both groups (Table 3). The reduction in diastolic blood pressure was similar for both groups, but systolic blood pressure reduction was about two-fold greater in the old group. The pulse pressure was significantly reduced compared with baseline values in the old group, but it remained unchanged in the young group. The increase in heart rate and reduction in LVET after nitroglycerin were similar between the two groups. Nitroglycerin similarly lowered carotid AI in both young and old groups. Fig. 2 shows a typical example of the carotid arterial contour before and after nitroglycerin in a young (upper panels) and an old patient (lower panels). In the young

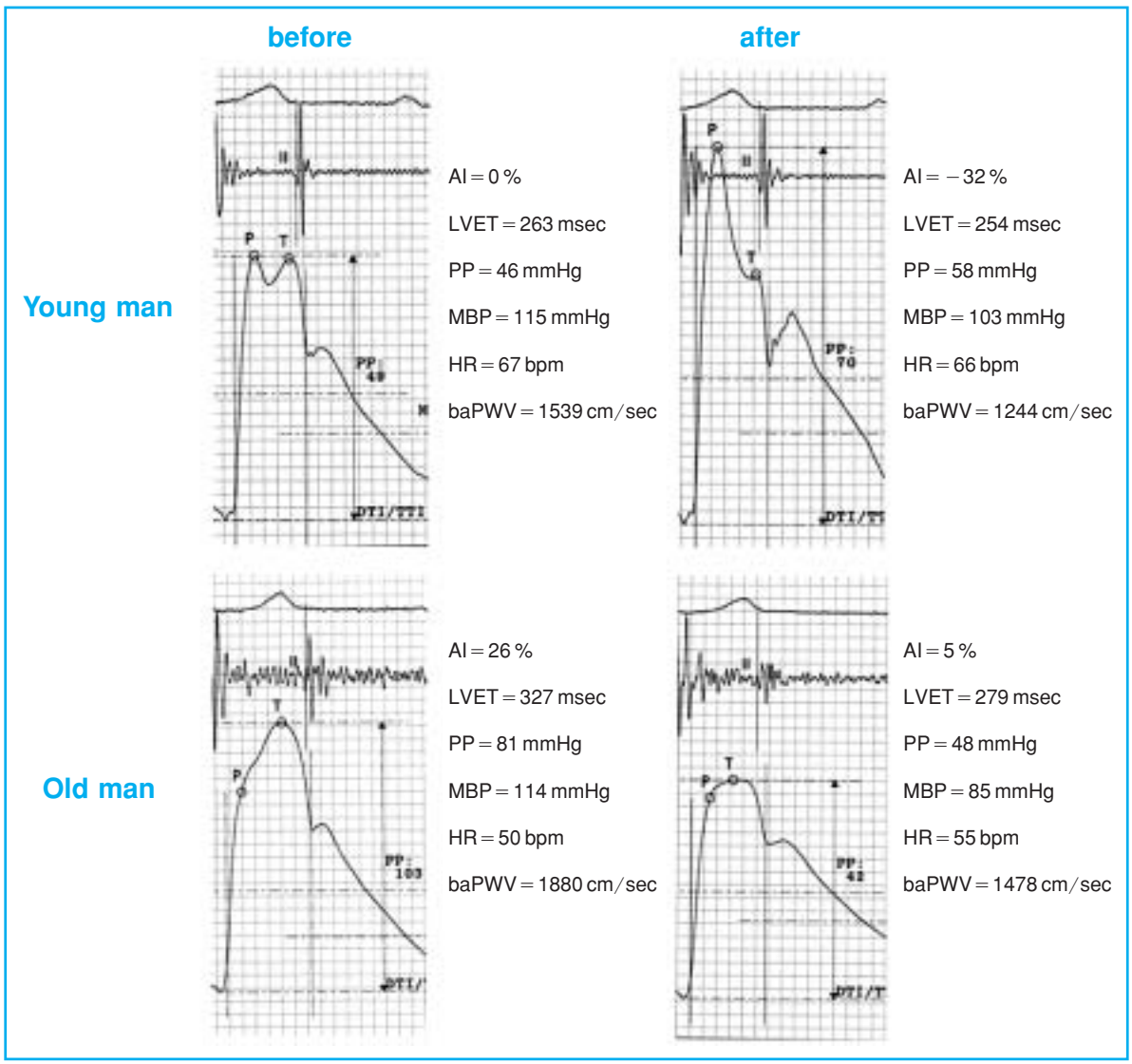


Fig. 2 Changes in carotid pulse contour before and after sublingual administration of nitroglycerin in young (upper panels) and old (lower panels) hypertensive men.
AI = augmentation index; LVET = left ventricular ejection time; PP = pulse pressure; MBP = mean blood pressure; HR = heart rate; baPWV = brachial-ankle pulse wave velocity

patient, nitroglycerin increased pulse pressure from 46 to 58 mmHg despite a marked reduction in AI (from 0% to −32%). The reduction in AI was associated with a marked increase in early systolic peak with only a minor reduction in late systolic peak.

In the old patient, nitroglycerin reduced pulse pressure from 81 to 48 mmHg. The reduction in AI from 26% to 5% was associated with a marked reduction in late systolic peak. The brachial-ankle PWV was significantly reduced compared with baseline values in both groups (Table 3). The reduction, however, was about 74% greater in the old group ($P<0.000001$) (Table 3). The change in pulse pressure after nitroglycerin was significantly correlated with the reduction in brachial-ankle PWV ($r=0.384$, $P<0.00005$) but was not correlated with the change in AI ($r=0.05$) in the old group (Table 4).

Table 4 Relationship between the changes in cardiovascular parameters and those in brachial-ankle PWV or AI in young and old hypertensive patients

	Young				Old			
	ΔbaPWV		ΔAI		ΔbaPWV		ΔAI	
	r	P	r	P	r	P	r	P
ΔSBP	0.147	n.s.	0.03	n.s.	0.503	<0.000001	0.276	<0.005
ΔDBP	0.07	n.s.	0.217	<0.05	0.237	<0.05	0.379	<0.0001
ΔMBP	0.238	<0.05	−0.006	n.s.	0.406	<0.00005	0.353	<0.0005
ΔPP	0.09	n.s.	−0.139	n.s.	0.384	<0.00005	0.05	n.s.
ΔHR	−0.017	n.s.	−0.402	<0.00001	0.101	n.s.	−0.431	<0.000005

baPWV = brachial-ankle pulse wave velocity; AI = augmentation index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; HR = heart rate

Discussion

Increased pulse pressure is now of great interest as a strong independent predictor for cardiovascular morbidity and mortality.[1–3] Increased pulse pressure means a progression of arterial aging and thus correlates with prognosis. Brachial-ankle PWV is a new measure for arterial stiffness that includes characteristics of both aorta and lower limb artery.[16] The relationship between the brachial-ankle PWV and pulse pressure is not fully understood. Moreover the relationship between arterial stiffness and pulse pressure would change with age. In light of this, we examined hemodynamic parameters, brachial-ankle PWV, and carotid AI in a large number of young and old hypertensive patients.

Hypertensive patients from the older group demonstrated a significantly greater pulse pressure than did young patients, although mean blood pressure did not differ. The increased pulse pressure was associated with higher brachial-ankle PWV and greater carotid AI. Moreover, pulse pressure was significantly and positively correlated with both brachial-ankle PWV and carotid AI. In multiple regression analyses, brachial-ankle PWV as well as mean blood pressure were significant contributors to the pulse pressure, but the AI was not. These data suggest that brachial-ankle PWV may be a better measure for arterial aging than AI in old hypertensive patients. In young hypertensive patients, only mean blood pressure was an independent contributor for pulse pressure, suggesting that systemic arterial stiffness depends mainly on transmural pressure.

Effects of sublingual administration of nitroglycerin on pulse pressure were very different between young and old patients. Nitroglycerin reduced systolic and diastolic blood pressures by the same degree in the young hypertensive group. In the older hypertensive group, systolic blood pressure was reduced by about two times more than diastolic blood pressure. Consequently, pulse pressure was significantly reduced in the older group while it remained unchanged in the young. Namely, nitroglycerin effectively reduced the increased pulse pressure in older hypertensive patients.

Two mechanisms may explain this result. First, it has been shown that nitroglycerin reduces the tone of small muscular arteries/arterioles.[11] These effects should shift the wave reflection site to more distal portion, delay the arrival of reflected wave, and reduce the intensity of wave reflection,[11] leading to a reduction in pulse pressure. In fact, diminution of pulse pressure was associated with a marked reduction in late systolic peak in the old patient, as shown in Fig. 2. Second, mean blood pressure was an independent

predictor for pulse pressure, independent of age. This finding means that an increase in the static component of blood pressure reduces aortic compliance and thereby increases the pulsatile component of blood pressure. In fact, compliance of large arteries is more sensitive to blood pressure change than is that of muscular arteries. Recently we have shown that carotid-femoral PWV increased by 2.4 times compared to femoral-ankle PWV in response to a similar degree of blood pressure increase.[16] In other words, mean blood pressure reduction by dilatation of muscular arterioles could predominantly increase the compliance of large arteries and reduce pulse pressure.

No change in pulse pressure despite a significant reduction in mean blood pressure in the younger group strongly suggests that some mechanisms counteracted the expected reduction in pulse pressure. As shown in Fig. 2, the young patient demonstrated an augmentation of early systolic peak after nitroglycerin. Consequently, pulse pressure was increased despite a decrease in mean blood pressure. It has been well known that early systolic peak depends both on ventricular ejection and large artery compliance. In our study, baseline heart rate did not differ between young and old patients. Moreover, LVET also was similar before and after administration of nitroglycerin; therefore, we suggest that the expected pulse pressure reduction was offset by aortic stiffening in the younger patients.

Our data are consistent with the recent report by Soma, et al.[21] They showed in 50-year-old hypertensive patients that nitroglycerin reduced mean blood pressure but did not change pulse pressure. These hemodynamic changes were associated with a significant reduction in wave reflection and increase in aortic characteristic impedance. They speculated that accelerated left ventricular ejection resulting from reflex sympathetic activation might offset the expected reduction in aortic stiffness. In our data, changes in pulse pressure after nitroglycerin were not related to the changes in heart rate or to those in LVET in the younger patients. We failed to clarify why arterial response to nitroglycerin differed between young and old hypertensive patients. This issue may be an important one to address in future studies.

Nitroglycerin reduced the brachial-ankle PWV by about 74% more in the older group compared to the younger group, implying that systemic arterial stiffness decreased more in the older patients. An alternative explanation, however, is that arterial stiffness was less improved by nitroglycerin in young hypertensives. It has been reported that the response of muscular arteries/arterioles to nitroglycerin is minimally affected by age.[22] Therefore, the lesser reduction in brachial-ankle PWV in the young group could be explained chiefly by the counter-reaction of large arteries.

We propose that simultaneous evaluation of carotid pulse contour is important to obtain deeper insight into the physiological significance of arterial stiffness measures. As noted above, reduction in AI after sublingual administration of nitroglycerin does not ensure the preferred change in the arterial system; a decrease in AI could be achieved not only by the reduction in late systolic peak, but also by an augmentation of early systolic peak. The latter change could increase the cardiac load and be harmful. We can visualize whether the reduction in AI is associated with truly preferable changes in arterial function through carotid pulse contour analysis.

This concept is also applicable to the evaluation of brachial-ankle PWV. The brachial-ankle PWV includes the properties of anatomically and physiologically different parts of the arterial tree, i.e., large elastic arteries and muscular arteries. Because the stiffness of each arterial part does not necessarily demonstrate parallel directional change, the net change in the brachial-ankle PWV does not correctly express the change in the property of the aorta. To examine if the reduction in brachial-ankle PWV is associated with the

reduction in aortic stiffness, observation of an early systolic peak of carotid pulse contour is helpful.

Finally this study provides two important clinical implications. First, heart rate was positively correlated with brachial-ankle PWV and negatively correlated with AI as previously reported.[23,24] These data raise the caution that in patients with extremely low or high heart rate, the brachial-ankle PWV and AI provide opposing data about arterial function; thus, we should take into account heart rate at the time of measurement in the evaluation of brachial-ankle PWV or AI. Second, the effective reduction of pulse pressure by nitroglycerin in old hypertensives strongly suggests that increase in pulse pressure with aging considerably depends on NO deficiency . Thus antihypertensive treatment to reduce pulse pressure should focus on improving endotherial function and thereby increasing NO availability.

In conclusion, in older hypertensive patients, the brachial-ankle PWV was an independent predictor for pulse pressure, but AI was not. Thus, systemic arterial stiffness seems to play a greater role in the regulation of pulse pressure than does wave reflection. To correctly understand the dynamic behavior of brachial-ankle PWV or AI after pharmacological interventions, simultaneous analysis of carotid pulse contour is helpful.

Acknowledgements

We would like to thank Mrs. Junko Sakuraba and Naomi Chiba for their technical assistance. We also thank Dr. Paul Kretchmer for his assistance in editing this manuscript. This study was supported in part by Grants-in-Aid from the Miyagi Prefectural Kidney Association, the Japan Arteriosclerosis Prevention Fund, and Japan Labour Health and Welfare Organization.

References

1. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. Hypertension. 1994;23:395–401.
2. Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension. 1998;32:560–564.
3. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. JAMA. 1999;281:634–639.
4. Mitchell GF. Pulse pressure, arterial compliance and cardiovascular morbidity and mortality. Curr Opin Nephrol Hypertens. 1999;8:335–342.
5. Franklin SS, Sutton-Tyrrell K, Belle SH, Weber MA, Kuller LH. The importance of pulsatile components of hypertension in predicting carotid stenosis in older adults. J Hypertens. 1997;15: 1143–1150.
6. Zanchetti A, Bond MG, Hennig M, et al. Risk factors associated with alterations in carotid intima-media thickness in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis. J Hypertens. 1998;16:949–961.
7. Pannier B, Brunel P, el Aroussy W, Lacolley P, Safar ME. Pulse pressure and echocardiographic findings in essential hypertension. J Hypertens. 1989;7:127–132.
8. Baguet JP, Mallion JM, Moreau-Gaudry A, Noirclerc M, Peoc'h M, Siche JP. Relationships between cardiovascular remodelling and the pulse pressure in never treated hypertension. J Hum Hypertens. 2000;14:23–30.
9. London GM, Guerin AP, Pannier B, Marchais SJ, Safar ME. Large artery structure and function in hypertension and end-stage renal disease. J Hypertens. 1998;16(12 Pt 2):1931–1938.
10. O'Rourke MF, Yaginuma T. Wave reflections and the arterial pulse. Arch Intern Med. 1984;144:366–371.
11. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ. Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. Hypertension. 2001;37: 1429–1433.
12. Munakata M, Ito N, Nunokawa T, Yoshinaga K. Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. Am J Hypertens. 2003;16(8):653–657.
13. Munakata M, Nagasaki A, Nunokawa T, Sakuma T, Kato H, Yoshinaga K, Toyota T. Effects of valsartan and nifedipine coat-core on systemic arterial stiffness in hypertensive patients. Am J Hypertens. 2004;17:1050–1055.
14. Munakata M, Sakuraba J, Tayama J, et al. The higher brachial-ankle pulse wave velocity is associated with more advanced carotid atherosclerosis in end-stage renal disease. Hypertens Res. 2005;28:9–14.
15. McDonald DA. Regional pulse-wave velocity in the arterial tree. J Appl Physiol. 1968;24(1):73–78.
16. Munakata M, Tayama J, Nunokawa T, Yoshinaga K, Toyota T. Brachial-ankle pulse wave velocity as a novel measure for arterial stiffness; present evidences and perspectives. Curr Hypertens Rev. 2005. (in press)
17. Cortez-Cooper MY, Supak JA, Tanaka H. A new device for automatic measurements of arterial stiffness and ankle-brachial index. Am J Cardiol. 2003;91(12):1519–1522,
18. Matsui Y, Kario K, Ishikawa J, Eguchi K, Hoshide S, Shimada K. Reproducibility of arterial stiffness indices (Pulse wave velocity and augmentation index) simultaneously assessed by automated pulse wave analysis and their associated risk factors in essential hypertensive patients. Hypertens Res. 2004;27:851–857.
19. Hasegawa M, Rodbard D, Kinishita Y. Timing of the carotid arterial sounds in normal adult men: measurement of left ventricular ejection, pre-ejection period and pulse transmission time. Cardiology. 1991;78:138–149.
20. Murashima M, Murashima M, Matii K, Yokoyama T. Effect of nitroglycerin spray (TY-0155) on plasma concentration of nitroglycerin, blood pressure and heart rate in healthy volunteers. Kiso to Rinsyo 1990;24(8):3881–3890.
21. Soma J, Angelsen BA, Techn D, Aakhus S, Skjaerpe T. Sublingual nitroglycerin delays arterial wave reflections despite

increased aortic "stiffness" in patients with hypertension: a doppler echocardiography study. J Am Soc Echocardiogr. 2000; 13(12):1100–1108.
22. Woo KS, McCrohon JA, Chook P, et al. Chinese adults are less susceptible than whites to age-related endothelial dysfunction. J Am Coll Cardiol. 1997;30:113–118.
23. Gatzka CD, Cameron JD, Dart AM, et al. Correction of carotid augmentation index for heart rate in elderly essential hypertensives. ANBP2 investigators. Australian comparative outcome trial of angiotensin-converting enzyme inhibitor- and diuretic-based treatment of hypertension in the elderly. Am J Hypertens. 2001;14:573–577.
24. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol. 2000;525:263–270.

Review Article

Morning Hypertension: A Pitfall of Current Hypertensive Management

JMAJ 48(5): 234–240, 2005

Kazuomi Kario*1

Abstract

Morning hypertension has recently attracted more attention because of the close relation between blood pressure levels in the early morning and cardiovascular risk. Cases of morning hypertension, i.e., higher blood pressure in the early morning than in the evening, are classified into two types: the "morning-surge" type, characterized by a marked increase in blood pressure in the early morning, and the "nocturnal-hypertension" type, characterized by high blood pressure that persists from nighttime until early morning. Although these two types are caused by different pathologic mechanisms, both result in hypertensive organ damage and increase cardiovascular risk. Control of morning hypertension can be regarded as the gateway to strict 24-hour blood pressure control. Standard antihypertensive treatment in accord with current guidelines, when combined with chronobiologic antihypertensive treatment focused on morning hypertension and guided by home blood pressure monitoring, seems to provide more effective prevention of cardiovascular events.

Key words Morning hypertension, Morning surge, Nocturnal hypertension, Cardiovascular risk, Chronobiological antihypertensive medication

Introduction

Morning hypertension has attracted a great deal of attention in recent years. Morning blood pressure (BP) levels measured at home are more closely associated with risk of damage to the brain, heart, and kidney, as well as with the risk of all cardiovascular events, than are BP levels measured at clinics. In addition, an increase in BP that occurs from nighttime to early morning (i.e., morning-surge BP) is highly likely to be a cardiovascular risk factor, independent of 24-hour BP levels. However, in current clinical practice, no adequate control of hypertension has been achieved; morning BP levels before dosing are increased in more than half of hypertensive patients on antihypertensive therapy, even if they are under relatively good BP control at clinics (Fig. 1).[1] Thus, morning hypertension is a challenge to the current clinical practice of hypertension.

This paper describes the diagnosis and treatment of morning hypertension in daily clinical practice, providing the most up-to-date data obtained in studies from Jichi Medical School.

*1 Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical School, Tochigi
Correspondence to: Kazuomi Kario MD, FAHA, FACC, FACP, Professor, Center of Excellence (COE) Program, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical School, 3311-1, Yakushiji, Minamikawachi-cho Kawachi, Tochigi 329-0431, Japan.
Tel: 81-285-58-7344, Fax: 81-285-44-5317, E-mail: kkario@jichi.ac.jp
This article is an updated and revised version of a paper published in the Journal of the Japan Medical Association, Vol.132, No.4, 2004, pages 554–559.

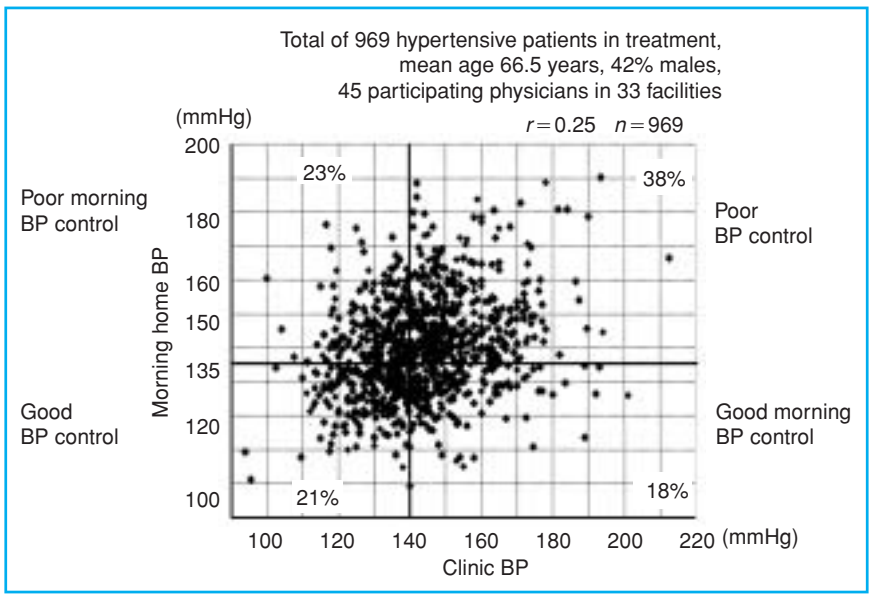


Fig. 1 Jichi morning hypertension research (J-MORE) study
(From Kario K, et al. Circulation. 2003;108:e72–e73)

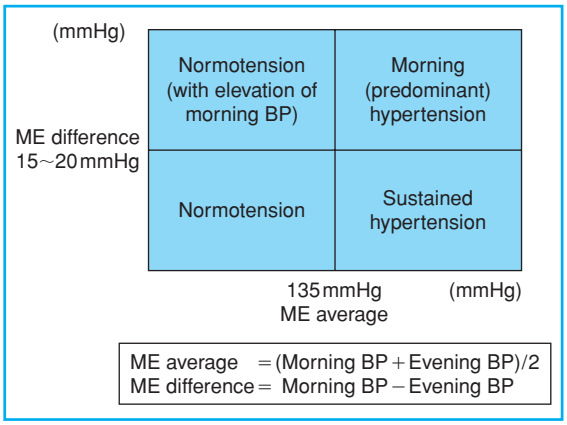


Fig. 2 Definition of morning hypertension using self-monitored home BP (Jichi Medical School)

Definition of Morning Hypertension

Recent clinical studies have shown that BP levels in the early morning are significantly associated with risk of damage to the brain, heart, and kidney as well as the risk of all cardiovascular events. The Ohasama Study, a longitudinal cohort study in which home BP was measured once every morning, showed that morning BP levels predicted cardiovascular death more accurately than randomly obtained BP levels in a general population of local residents in Japan.[2]

We use the definition of morning hypertension based on BP measurements in the early morning and at bedtime (Fig. 2).[3] There is a consensus that, when home BP is used to exclude white-coat hypertension, an average of multiple home BP measurements should be used. Therefore, we exclude cases of whitecoat hypertension using a cut-off value of 135 mmHg for averaged BP values in the morning and evening [morningness-eveningness (ME) average]. After that, patients are divided into sustained hypertension and morning (predominant) hypertension according to a difference (ME difference) in BP of 15–20 mmHg. That is, patients with morning (predominant) hypertension are those with high average values for morning and evening BP and prominent variations in morning and evening BP. In contrast, hypertensive patients who show only slight differences between morning and evening BP values are considered to have sustained hypertension.

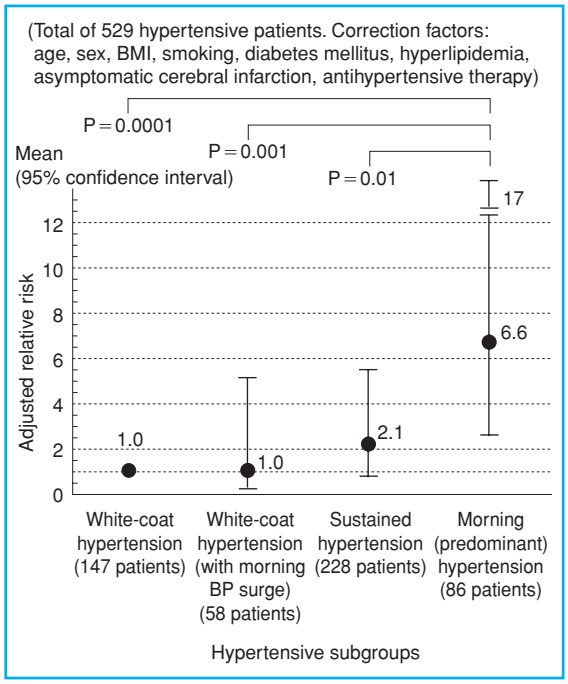


Fig. 3 Stroke risk of Japanese hypertensive patients (JMS ABPM study, Wave 1)

[Kario K, et al. Morning hypertension. (in preparation)]

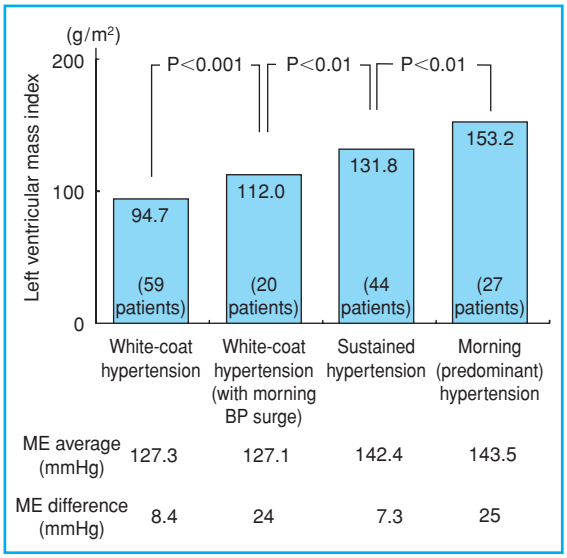


Fig. 4 Morning hypertension and left ventricular hypertrophy in hypertensive patients on antihypertensive treatment

(Kuroda T, Kario K, et al. Presented at the 26th Annual Scientific Meeting of the Japanese Society of Hypertension on Oct. 31, 2003)

Figure 3 shows the risk of stroke in Japanese hypertensive patients, based on our definition of morning (predominant) hypertension. In the Jichi Medical School Ambulatory Blood Pressure Monitoring (JMS ABPM) study (Wave 1) in elderly Japanese patients with hypertension, we followed 519 patients without a history of evident cardiovascular events (mean age, 72 years) for a mean of 41 months for possible onset of cardiovascular events. The patients underwent brain MRI and 24-hour ambulatory blood pressure monitoring (ABPM) at baseline.[4] In this study, the ME average and ME difference were independently associated with stroke risk.[5] Patients with white-coat hypertension who showed only slight variations in morning and evening BP were used as controls, with cut-off values of ME average (systolic pressure) and ME difference (systolic pressure) being 135 mmHg and 20 mmHg, respectively. As a result, stroke risk was about 2-fold for sustained hypertension and 6.6-fold for morning (predominant) hypertension.[3] Among patients with white-coat hypertension with a low ME average, there was no increase in stroke risk for those with morning BP surge.

We have also performed an echocardiographic study of hypertensive patients who are under treatment to evaluate hypertensive heart disease and determine its relationship with the state of home BP control. The results showed that the left ventricular mass index was greater in patients with morning (predominant) hypertension than in those with sustained hypertension, indicating advanced left ventricular hypertrophy (Fig. 4).

From the above results, we consider that our definitions of sustained hypertension and morning (predominant) hypertension based on home BP measurement are helpful for the management of hypertension in truly hypertensive patients, excluding cases of white-coat hypertension.

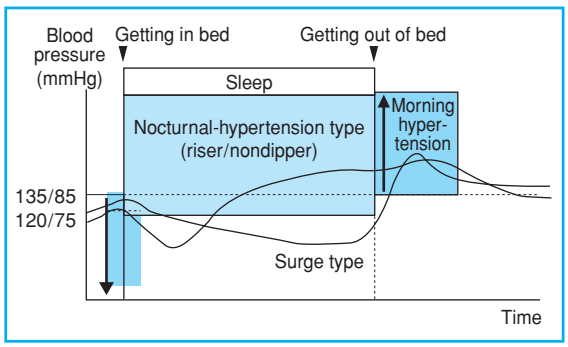


Fig. 5 Abnormal diurnal variation in blood pressure in two types of morning (predominant) hypertension

Two Types of Morning Hypertension

Prominent morning hypertension that is highly reproducible with a home BP monitor can be classified into two types according to BP levels at night determined by 24-h monitoring (Fig. 5), namely, nocturnal hypertensive morning hypertension and morning-surge hypertension. The former type presents a shift from nocturnal hypertension and includes non-dippers, with a diminished nocturnal fall in BP, and risers, with nocturnal levels higher than daytime levels. The latter group is characterized by BP elevation beginning about 2 hours before getting out of bed, followed by further elevation after rising from bed. Both riser-type hypertension and morning-surge hypertension serve as independent risk factors for stroke. Conditions presumed to be associated with these two types of morning hypertension are listed in Table 1.[6]

1. Morning hypertension of the nocturnal hypertensive type

The cardiovascular risk of risers is highest, involving fatal stroke—particularly cerebral hemorrhage—and cardiac events including sudden cardiac death.[7–9] Insufficient nocturnal depression by short-acting antihypertensive drug therapy in hypertensive patients induces morning hypertension of this nocturnal hypertensive type.[10] In addition, patients with diabetes mellitus, poststroke state, cardiac failure, and sleep apnea syndrome frequently have this type of morning hypertension. However, investigations of the time of onset of cardiovascular events in diabetic patients have found no diurnal variation in onset. In other words, the increased risk of morbidity due to morning hypertension occurs in the nighttime, and the increased risk in the early morning is an extension of nighttime risk.

Table 1 Conditions associated with morning hypertension

Nocturnal-hypertension (riser/nondipper) type
Increased intravascular volume (heart failure, renal failure, etc.)
Abnormal autonomic nervous system (diabetes, parkinsonism, Shy-Drager syndrome, cardiac transplantation, orthostatic hypotension, etc.)
Secondary hypertension (pheochromocytoma, primary aldosteronism, Cushing's syndrome, etc.)
Salt-sensitive hypertension
Sleep disorders (sleep apnea syndrome, etc.)
Metabolic syndrome (obesity)
Depressive state
Dementia
Elderly patients
Black male patients
Hypertensive target organ damage [cerebral infarction, asymptomatic cerebrovascular disorder (silent cerebral infarcts, deep white matter lesions), cardiac hypertrophy, proteinuria, microalbuminuria, etc.]
Surge type
Elderly patients
Orthostatic hypertension
Sleep disorders (sleep apnea syndrome, etc.)
Hypertensive target organ damage [cerebral infarction, asymptomatic cerebrovascular disorders (silent cerebral infarcts, deep white matter lesions), cardiac hypertrophy, proteinuria, microalbuminuria, etc.]
α-Sympathetic hyperactivity
Dehydration
Large artery stiffness
Baroreceptor dysfunction

2. Surge-type morning hypertension

Although it has been suggested that morning BP surge may be involved in the onset of cardiovascular events, whether or not it is an actual risk for cardiovascular events has not been clarified. Based on the results of the

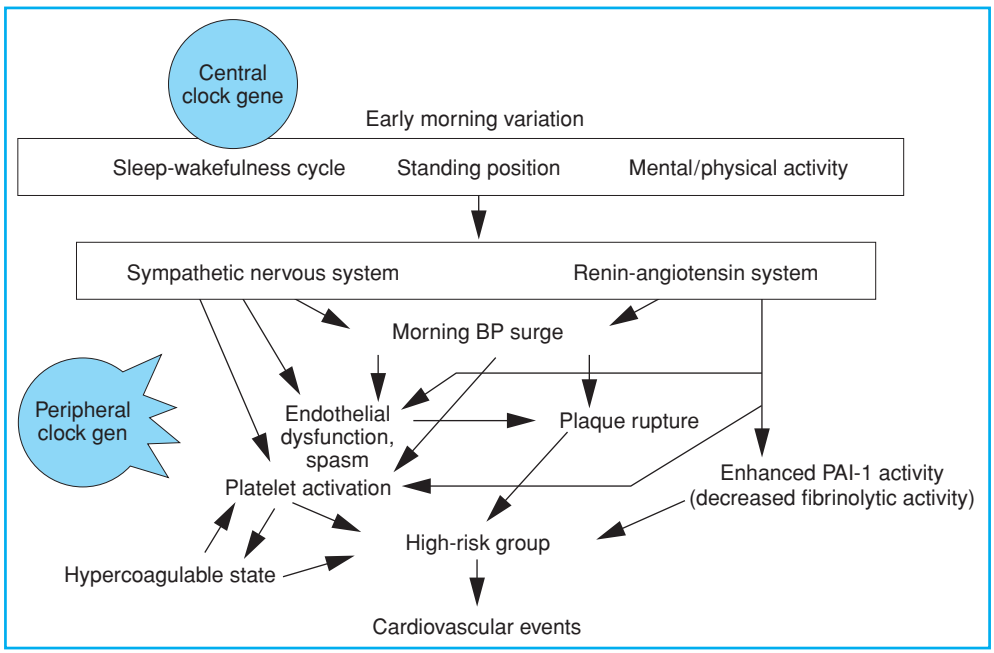


Fig. 6 Mechanism of the morning onset of cardiovascular events
[Kario K, et al. J Cardiovasc Pharmacol. 2003;42(Suppl 1):S87–S91]

JMS ABPM study, we reported that morning BP surge is associated with silent cerebral infarcts and represents a risk for cerebrovascular disorders.[4] In this study, both early morning BP levels and morning BP surge were important as risk factors for stroke.

In regard to the relationship with hypertensive heart disease, Kuwashima et al. first demonstrated in a study examining elderly patients with hypertension that morning BP surge measured at the time of rising from bed is correlated with the left ventricular weight coefficient obtained from echocardiogram.[11] In addition, hypertensive patients with morning surge are reported to show an increase in the ratio of the low- to high-frequency element of heart rate—an index of sympathetic activity level—as well as prolonged QTc interval and increased QTc dispersion.[12] These findings suggest that patients with morning surge have considerable variability in electric excitation at the myocardial level in response to sympathetic activity, and thus are prone to develop arrhythmia. A relationship between morning BP surge and early diabetic nephropathy has also been reported.[13]

Mechanism of Target Organ Damage

In the early morning, not only blood pressure but also other cardiovascular risk factors including cardiovascular response and thrombotic tendency are worsened, leading to the occurrence of cardiovascular events in the early morning (Fig. 6).[14] The morning surge in BP is influenced by the sympathetic nerve system and renin-angiotensin system. Healthy individuals also experience morning BP surge as a physiological phenomenon, but a prominent increase in BP leads to the risk of cardiovascular events. Morning BP surge itself places a direct load on the vascular wall and causes an increase in shear stress as a result of increased blood flow, leading to an increased likelihood of vascular wall spasm and rupture of plaque. At the site of vascular stenosis resulting from atherosclerosis, high shear stress is present, and platelets are activated. Because of this, increased platelet

aggregation may be triggered in the early morning as a result of morning BP surge. Further, tissue plasminogen activator inhibitor 1 (PAI-1), a fibrinolysis inhibitor, is elevated in the early morning, increasing the risk of symptomatic and asymptomatic cardiovascular disease.[15]

Recent years have seen remarkable progress in molecular biologic studies in the area of chronobiology. In 1997, the first mammalian clock gene was cloned from the mouse hypothalamus. It was reported that this gene forms a central biological clock. In addition, it became apparent that the clock gene is expressed not only in the central nervous system but also in peripheral tissue, where it is present in the cells. The central clock synchronizes each peripheral clock and thereby regulates the circadian rhythm of the body. It is presumed that the circadian rhythm of the cardiovascular system is under the influence of both the central clock and the peripheral clock present in cardiovascular tissue. Questions relating to the involvement of the clock gene in peripheral tissue to the increasing risk of cardiovascular events in the early morning, as well as the extent of this involvement, are important subjects of future investigation.

Treatment of Morning Hypertension

Since not only blood pressure but also various other cardiovascular risk factors are aggravated in the early morning, antihypertensive treatment for morning hypertension is likely to offer greater benefit in preventing cardiovascular events. Hypertensive patients on standard antihypertensive treatment often have morning hypertension of the nocturnal-hypertension type because the effect of most antihypertensive drugs does not last for 24 hours. Antihypertensive treatment targeting morning hypertension combined with standard treatment may enable more effective prevention of cardiovascular events.

The first step in the treatment of morning hypertension in clinical practice is for the patient to self-monitor early morning BP at home. In addition, in patients with prominent morning hypertension in whom the difference between morning and evening systolic BP is more than 15–20 mmHg, it is important to determine by ambulatory blood pressure monitoring whether the hypertension is of the nocturnal-hypertension type or the morning-surge type. Specifically, it is recommended to combine non-specific and specific antihypertensive treatments as shown in Fig. 7, to control morning BP levels to achieve an average of morning (before dosing) and evening (at bedtime) BP of under 135/85 mmHg and a morning-evening pressure difference of less than 15–20 mmHg.

In principle, a long-acting antihypertensive drug whose effect lasts for 24 hours initially is used as non-specific treatment. This therapy is aimed at reducing the ME average to less than 135 mmHg (systolic pressure). Typical drugs used in this therapy include long-acting calcium antagonists[16,17] and diuretics. However, even antihypertensive drugs designed for once-daily doses are rarely effective from the morning dosing

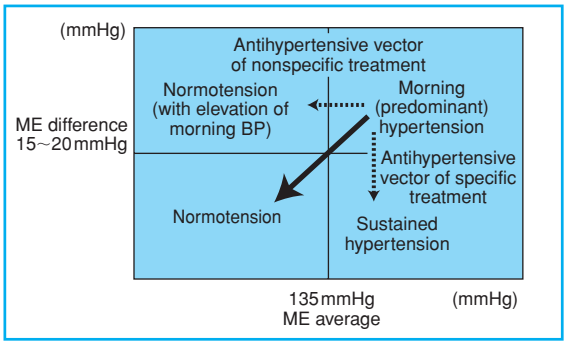


Fig. 7 Specific antihypertensive treatment for morning (predominant) hypertension using home BP monitoring

Nonspecific treatment: long-acting antihypertensive drugs (twice-daily, morning and evening, doses should also be considered), diuretics

Specific treatment: α-blockers used at bedtime

Renin-angiotensin-aldosterone system inhibitors (dosing at bedtime should also be considered)

Heart rate-controlling calcium antagonists (cilnidipine, azelnidipine, diltiazem)

until the following morning, with individual differences noted in the duration of the antihypertensive effect. When the ME difference exceeds 15–20 mmHg after actual prescription, dosing in both the morning and evening (or at bedtime) may be more useful.

Specific treatment includes inhibitors of the sympathetic nervous system and renin-angiotensin system, which show aggravation in the early morning. Administration of α-blockers at bedtime provides a relatively specific reduction in early morning BP.[18,19] β-Blocker monotherapy does not cause a specific decrease in early morning BP. Since the renin-angiotensin system is augmented in the early morning, treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists can be considered specific treatment.[20,21] However, for some drugs, the antihypertensive effect of one morning dose may not last until the following morning. In such cases, two divided daily doses or one daily dose at bedtime may be useful.[21] Recently, calcium antagonists such as cilnidipine, azelnidipine, and diltiazem have been used as specific treatments because they have an inhibitory effect on increasing heart rate.

Conclusion

For more effective prevention of cardiovascular diseases, the use of a chronobiological approach that targets morning hypertension and employs home BP monitoring is recommended in addition to standard antihypertensive treatment according to current guidelines.

References

1. Kario K, Eguchi K, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives. Response. Circulation. 2003; 108:e72–e73.
2. Ohkubo T, Imai Y, Tsuji I, et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. J Hypertens. 1998;16:971–975.
3. Kario K, Pickering TG, Shimada K, et al. Morning hypertension. (in preparation)
4. Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation. 2003;107:1401–1406.
5. Kario K, Eguchi K, Umeda Y, et al. Morning blood pressure surge and the risk of stroke. Circulation. 2003;108:e110–e111.
6. Kario K, Eguchi K, Hoshide S. et al. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. J Am Coll Cardiol. 2002;40:133–141.
7. Kario K, Pickering TG, Matsuo T, et al. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension. 2001;38:852–857.
8. Kario K, Shimada K, Pickering TG. Abnormal nocturnal blood pressure falls in elderly hypertension: clinical significance and determinants. J Cardiovasc Pharmacol. 2003;41(Suppl 1):S61–S66.
9. Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. J Hypertens. 2002;20:2183–2189.
10. Chonan K, Hashimoto J, Ohkubo T, et al. Insufficient duration of action of antihypertensive drugs mediates high blood pressure in the morning in hypertensive population: the Ohasama study. Clin Exp Hypertens. 2002;24:261–275.
11. Kuwajima I, Mitani K, Miyao M, et al. Cardiac implications of the morning surge in blood pressure in elderly hypertensive patients: relation to arising time. Am J Hypertens. 1995;8:29–33.
12. Marfella R, Gualdiero P, Siniscalchi M, et al. Morning blood pressure peak, QT intervals, and sympathetic activity in hypertensive patients. Hypertension. 2003;41:237–243.
13. Caramori ML, Pecis M, Azevedo MJ. Increase in nocturnal blood pressure and progression to microalbuminuria in diabetes. N Engl J Med. 2003;348:261–264.
14. Kario K, Shimada K, Pickering, TG. Clinical implication of morning blood pressure surge in hypertension. J Cardiovasc Pharmacol. 2003;42(Suppl 1):S87–S91.
15. Kario K, Matsuo T, Kobayashi H, et al. Hyperinsulinemia and hemostatic abnormalities are associated with silent lacunar cerebral infarcts in elderly hypertensive subjects. J Am Coll Cardiol. 2001;37:871–877.
16. Kario K, Shimada K. Differential effects of amlodipine on ambulatory blood pressure in elderly hypertensive patients with different nocturnal reductions in blood pressure. Am J Hypertens. 1997;10:261–268.
17. Eguchi K, Kario K, Hoshide Y, et al. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. Am J Hypertens. 2004;17:112–117.
18. Kario K, Schwartz JE, Pickering TG. Changes of nocturnal blood pressure dipping status in hypertensives by nighttime dosing of alpha-adrenergic blocker, doxazosin: results from the HALT Study. Hypertension. 2000;35:787–794.
19. Kario K, Pickering TG, Hoshide S, et al. Morning blood pressure surge and hypertensive cerebrovascular disease: role of the α-adrenergic sympathetic nervous system. Am J Hypertens. 2004; 17:668–675.
20. Eguchi K, Kario K, Shimada K. Comparison of candesartan with lisinopril on ambulatory blood pressure and morning surge in patients with systemic hypertension. Am J Cardiol. 2003;92: 621–624.
21. Kuroda T, Kario K, Hoshide S, et al. Effects of bedtime vs morning administration of the long-acting lipophilic angiotensin-converting enzyme inhibitor trandolapril on morning blood pressure in hypertensive patients. Hypertens Res. 2004;27:15–20.

Case Report

A Case Study of Remnant Gastric Ulcer: Eradication of *Helicobacter pylori* Not Only Improved the Ulcer But Also Decreased p53 Protein Expression

JMAJ 48(5): 241–245, 2005

Yoshio Ishibashi,[*1] Yutaka Suzuki,[*1] Nobuo Omura,[*1] Katsutoshi Kobayashi,[*1]
Atsuo Shida,[*1] Hideyuki Kashiwagi,[*1] Nobuyoshi Hanyu,[*1]
Mitsuyoshi Urashima,[*2] Katsuhiko Yanaga[*1]

Abstract

In this paper, we report the experience of a 66 year old man with remnant gastric ulcer 1 year after distal gastrectomy for early gastric cancer. First, H_2 antagonist therapy was applied but failed. Next, antibiotics therapy was applied to eradicate *Helicobacter pylori*. After the treatment, not only was *Helicobacter pylori* eradicated and the stage of ulcer improved, but also the oncosuppressor p53 protein expressed in gastric mucosa had decreased to undetectable levels. Chronic bile reflux is believed to increase the risk of ulcerative lesions in remnant stomach, but this case suggests that *Helicobacter pylori*-infection may also contribute to the etiology of remnant gastric ulcer.

Key words Remnant gastric ulcer, *H. pylori*, p53, Eradication

Introduction

Patients who have undergone distal gastrectomy for gastric ulcer or cancer are at risk of developing gastric ulcer and/or cancer in the remnant stomach.[1,2] Chronic bile reflux is believed to increase the risk of lesions in the remnant stomach.[3] Although *Helicobacter pylori* (*H. pylori*) is considered one of the major etiological agents for gastric cancer,[4] this is not necessarily true for remnant gastric lesions.[5,6]

We experienced a case where a remnant gastric ulcer which occurred after a partial gastrectomy for early gastric cancer responded well to eradication of *H. pylori*. In addition, p53 protein expressed in mucosal cells around the ulcer disappeared after eradication of *H. pylori*.

Onset and Course of the Case (Fig. 1)

A 66 year old man visited our hospital because of epigastralgia without specific histories in his past or in his family. The patient was diagnosed as having an early stage of gastric cancer and a pylorus side partial gastrectomy was performed, followed by Billroth I reconstruction on February 3, 2000. The lesion was 19×13 mm in size and classified as Type 0-IIc. The histology was

*1 Department of Surgery, Jikei University School of Medicine, Tokyo
*2 Division of Clinical Research & Development, Jikei University School of Medicine, Tokyo
Correspondence to: Yoshio Ishibashi MD, PhD, Department of Surgery, Jikei University School of Medicine, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo, Japan. Tel: 81-3-3433-1111, Fax: 81-3-5472-4140, E-mail: ishibashi@jikei.ac.jp

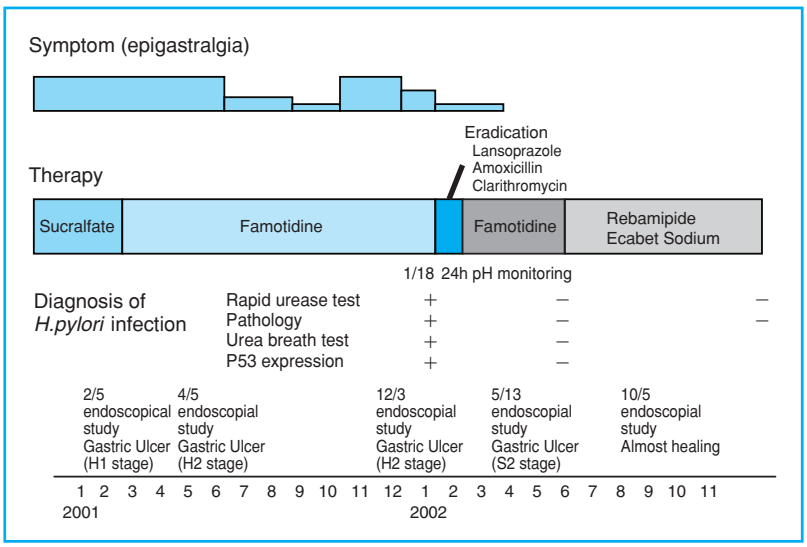


Fig. 1 Clinical course of the patient

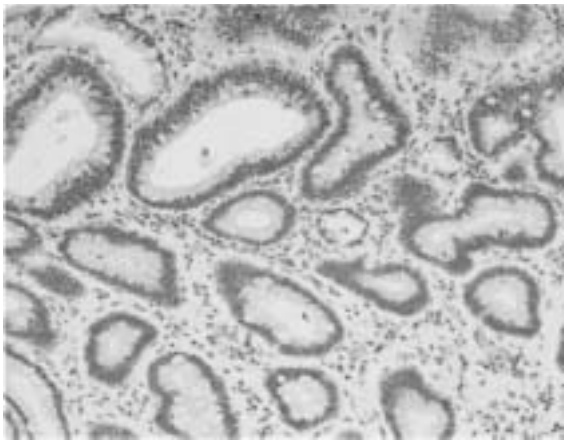


Fig. 2 p53 protein staining using the paraffin embedded cancer specimen obtained during the operation on Feb. 3, 2000

well-differentiated adenocarcinoma and considered as fStage IA (fT1, N0, H0, P0, M0) or Stage IA (T1N0M0) in TNM staging. Expression of p53 protein was negative in the paraffin embedded specimen (Fig. 2).

During follow-up at the outpatient clinic, the epigastralgia reemerged around January 2001. Upper endoscopic examination revealed a remnant gastric ulcer (H1 stage) in the residual stomach on February 5, 2001 (Fig. 3A). After starting therapy with H_2 receptor antagonists, his epigastralgia was partially improved. However, he visited our hospital again because of worsened epigastralgia. Existence of his remnant gastric ulcer was confirmed under endoscopic examination on December 3, 2001 (Fig. 3B). He was diagnosed with a positive *H. pylori*-infection by rapid urease test, ^{13}C-urea breath test and pathological findings. In addition, p53 protein was highly expressed in mucosal cells by immunohistostaining (Fig. 3C). To measure

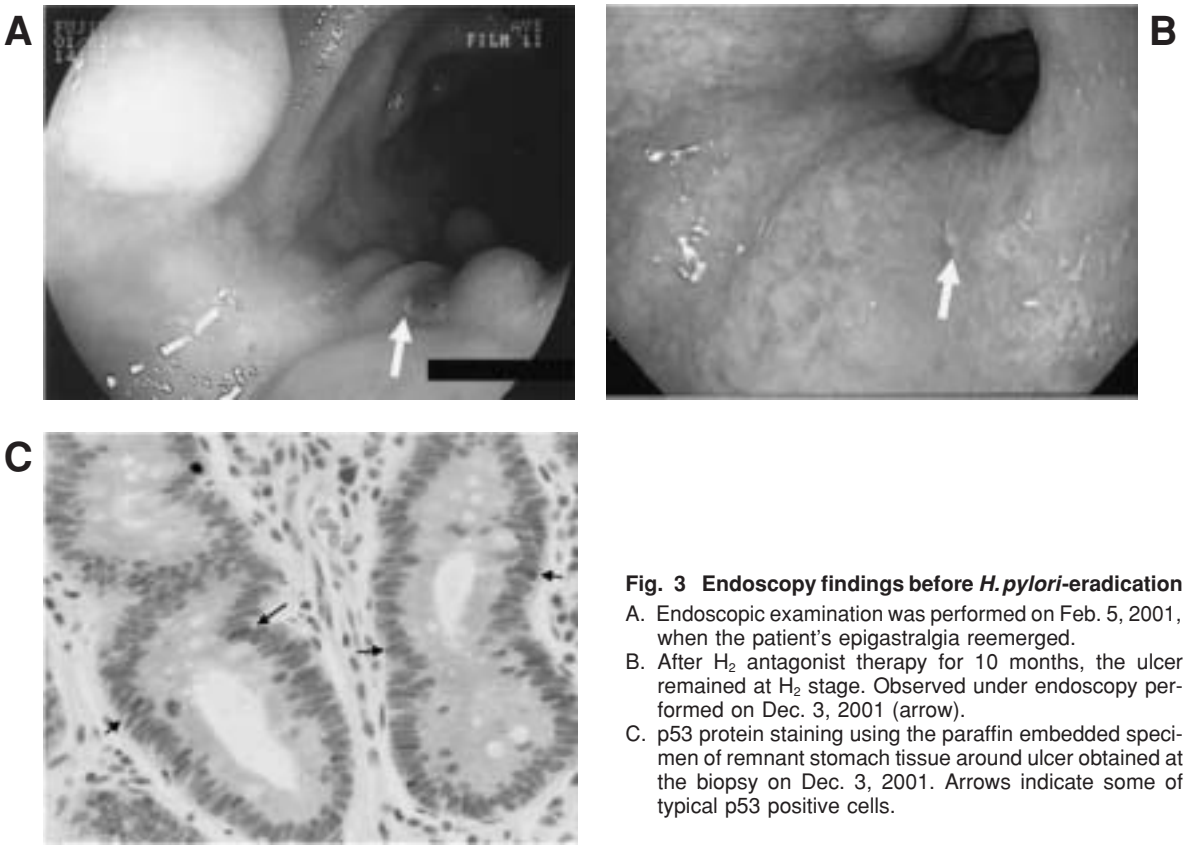


Fig. 3 Endoscopy findings before *H. pylori*-eradication

A. Endoscopic examination was performed on Feb. 5, 2001, when the patient's epigastralgia reemerged.
B. After H_2 antagonist therapy for 10 months, the ulcer remained at H_2 stage. Observed under endoscopy performed on Dec. 3, 2001 (arrow).
C. p53 protein staining using the paraffin embedded specimen of remnant stomach tissue around ulcer obtained at the biopsy on Dec. 3, 2001. Arrows indicate some of typical p53 positive cells.

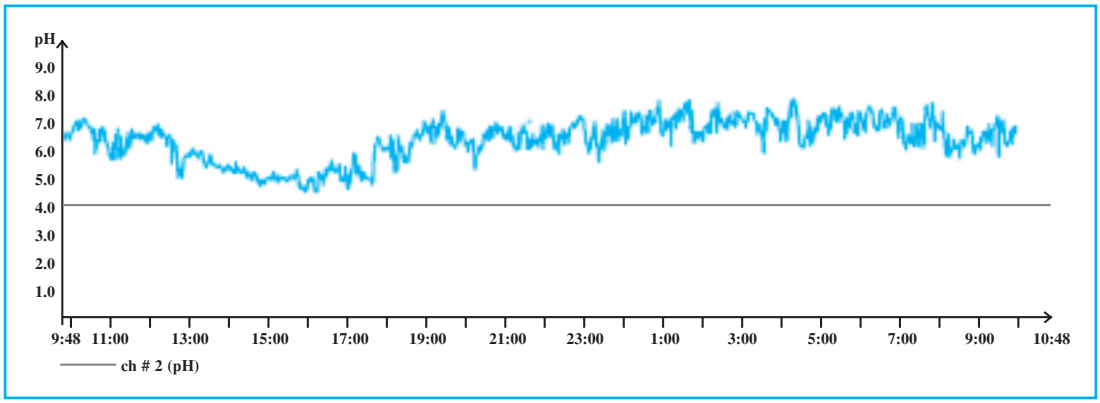


Fig. 4 pH monitoring for 24 hours in remnant stomach performed on Jan. 18, 2001

Intragastric pH was above 4.0 for 24 hours.

secretion of gastric acid, pH in the remnant stomach was monitored for 24 hours (Fig. 4). However, intragastric pH remained above 4.0 for 24 hours without administration of H_2 antagonist.

The patient had per-oral administration of lansoprazole, amoxicillin and clarithromycin for 1 week from January 22, 2002. After one month, the signs of epigastralgia improved. On May 13, 2002, the remnant

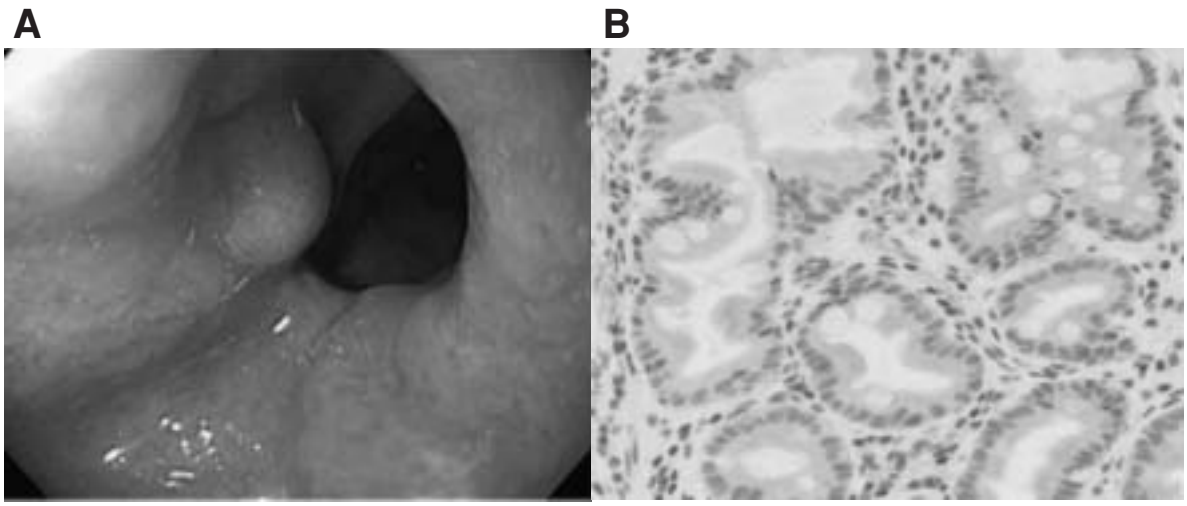


Fig. 5 Endoscopy findings after *H. pylori*-eradication

A. Endoscopic examination was performed on May 13, 2001. The ulcer had improved to S2 stage.
B. p53 protein staining using the paraffin embedded specimen of remnant stomach tissue around ulcer obtained at the biopsy on the same day. No p53 positive cells were observed.

gastric ulcer was improved to the S2 stage under endoscopic examination (Fig. 5A) and *H. pylori* infection was confirmed to be negative by rapid urease test, ^{13}C-urea breath test and pathological findings. Moreover, p53 protein was changed to negative in the mucosal cells of the stomach in the biopsy specimen (Fig. 5B). The lesion of remnant stomach has remained stable to date: March 2005.

Discussion

The remnant gastric ulcer studied in this case improved with eradication of *H. pylori*. In explaining the risk of ulcer or cancer occurring in the remnant stomach after partial gastrectomy, the theory of chronic bile reflux is widely held,[5] whereas the theory of infection with *H. pylori* is considered secondary, or not accepted.[6,7] Evidence that Billroth II reconstruction was worse than Roux-Y reconstruction and Billroth I in preventing remnant gastritis because it enhanced duodenogastric reflux may support the theory of chronic bile reflux.[8] However, recently duodenogastric reflux was demonstrated to facilitate the survival of *H. pylori* in the remnant gastric lesion after a distal gastrectomy.[9] Moreover, proton pump inhibitor-based therapy was effective for *H. pylori* eradication from the remnant stomach; on the other hand, eradication of *H. pylori* with antibiotics resulted in a significant decrease in inflammatory cell infiltration of the mucosal layer of the remnant stomach.[10] These suggest that both chronic bile reflex and *H. pylori*-infection may synergically induce lesions in the remnant stomach.

Although p53 was not expressed in the lesion of gastric cancer, it emerged in mucosal cells around the remnant gastric ulcer in this case. Of interest, expression of p53 decreased to below detectable levels after eradication of *H. pylori*. A previous study found that the accelerated cell turnover in the gastric epithelial cell induced by *H. pylori* infection was associated with p53 overexpression.[12] It is considered that expression of p53 in the gastric mucosa may result from DNA damage induced by *H. pylori* infection.[12] After eradication of *H. pylori*, the accumulation of p53 decreased and the reduction of inflammation was detected in the stomach mucosa.[13,14]

These results suggest that *H. pylori* is considered one of the major etiological agents for gastric lesions. In contrast, it was reported that *H. pylori* infection might not play an important role in the pathogenesis of recurrent ulcers after partial gastrectomy.[5] However, the case presented in this report demonstrated that eradication of *H. pylori* had occurred simultaneously with decreased expression of p53 as well as morphological improvement of the ulcerative lesion.

This case suggests that *Helicobacter pylori*-infection may contribute to the etiology of remnant gastric ulcer, although chronic bile reflux is believed to increase the risk of lesions in the remnant stomach. Further investigation is necessary to clarify the effects of *H. pylori*-eradication on preventing remnant gastric ulcer and/or cancer.

References

1. Takeda J, Hashimoto K, Koufuji K, Tanaka T, Kodama I, Kakegawa T. Remnant-stump gastric cancer following partial gastrectomy. Hepatogastroenterology. 1992;39:27–30.
2. Onodera H, Tokunaga A, Yoshiyuki T, et al. Surgical outcome of 483 patients with early gastric cancer: prognosis, postoperative morbidity and mortality, and gastric remnant cancer. Hepatogastroenterology. 2004;51:82–85.
3. Zhang C, Liu ZK, Yu PW. Effects of bile reflux and intragastric microflora changes on lesions of remnant gastric mucosa after gastric operation. World J Gastroenterol. 2004;10:1537–1539.
4. Uemura N, Okamoto S, Yamamoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med. 2001;345:784–789.
5. Huang WH, Wang HH, Wu WW, Lai HC, Hsu CH, Cheng KS. *Helicobacter pylori* infection in patients with ulcer recurrence after partial gastrectomy. Hepato-gastroenterol. 2004;51:1551–1553.
6. Leivonen MK, Haglund CH, Nordling SF. *Helicobacter pylori* infection after partial gastrectomy for peptic ulcer and its role in relapsing disease. Eur J Gastroenterol Hepatol. 1997;9:371–374.
7. Zhang C, Liu ZK, Yu PW. Effects of bile reflux and intragastric microflora changes on lesions of remnant gastric mucosa after gastric operation. World J Gastroenterol. 2004;10:1537–1539.
8. Osugi H, Fukuhara K, Takada N, Takemura M, Kinoshita H. Reconstructive procedure after distal gastrectomy to prevent remnant gastritis. Hepatogastroenterology. 2004;51:1215–1218.
9. Nakagawara H, Miwa K, Nakamura S, Hattori T. Duodenogastric reflux sustains *Helicobacter pylori* infection in the gastric stump. Scand J Gastroenterol. 2003;38:931–937.
10. Matsukura N, Tajiri T, Kato S, et al. *Helicobacter pylori* eradication therapy for the remnant stomach after gastrectomy. Gastric Cancer. 2003;6:100–107.
11. Kawabe A, Shimada Y, Uchida S, et al. Expression of cyclooxygenase-2 in primary and remnant gastric carcinoma: comparing it with p53 accumulation, *Helicobacter pylori* infection, and vascular endothelial growth factor expression. J Surg Oncol. 2002;80:79–88.
12. Jones NL, Shannon PT, Cutz E, et al. Increase in proliferation and apoptosis of gastric epithelial cells early in the natural history of *Helicobacter pylori* infection. Am J Pathol. 1997;151:1695–1703.
13. Satoh K, Kihira K, Kawata H, et al. p53 expression in the gastric mucosa before and after eradication of *Helicobacter pylori*. Helicobacter. 2001;6:31–36.
14. Hibi K, Mitomi H, Koizumi W, et al. Enhanced cellular proliferation and p53 accumulation in gastric mucosa chronically infected with *Helicobacter pylori*. Am J Clin Pathol. 1997;108:26–34.

The Concept and Practice of International Health in the Takemi Program

JMAJ 48(5): 246–255, 2005

Michael R Reich*1

Abstract

The Takemi Program in International Health was established at the Harvard School of Public Health in 1983 as a research and advanced training program for mid-career health professionals concerned with the allocation of resources for health, especially in developing countries. This essay describes the origins of the Takemi Program and presents seven principles that underlie the concept and practice of international health, as developed over the past two decades in the Takemi Program. The principles are: research emphasis, policy orientation, interdisciplinary perspective, mutual respect, individual freedom, community spirit, and individual capacity building. These principles provide the foundation for the collaboration between the Japan Medical Association and the Takemi Program since 1994. The broader implications of these principles are suggested for efforts to redefine the concept of international health.

Key words International health, Takemi Program in International Health, Public health practice, International cooperation

Introduction

In the twentieth century, the concept and practice of international health have been interpreted as evolving through five phases: from the treatment of tropical diseases by colonial powers within their foreign territories, to an emphasis on the control of infectious diseases across borders, to regional efforts at disease control and preventive medicine, to the establishment of the World Health Organization to promote a broad concept of health, to a more encompassing mission of achieving an equitable development through primary health.[1] An understanding of how international health unfolded in the last century, in both concept and practice, can help current efforts underway to redefine the concept of international health as we enter the twenty-first century.

Over the past twenty years, the Takemi Program in International Health at the Harvard School of Public Health has helped to develop the concept and practice of international health in a unique three-way collaboration between Japan, the United States, and developing countries. This article presents the origins and principles of the Takemi Program, to suggest some directions for a new international health.

*1 Harvard School of Public Health, Boston, USA
Correspondence to: Michael R Reich PhD, Taro Takemi Professor of International Health Policy, and Director of the Takemi Program in International Health, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA.
Tel: 617-495-2021, Fax: 617-495-5418, E-mail: michael_reich@harvard.edu

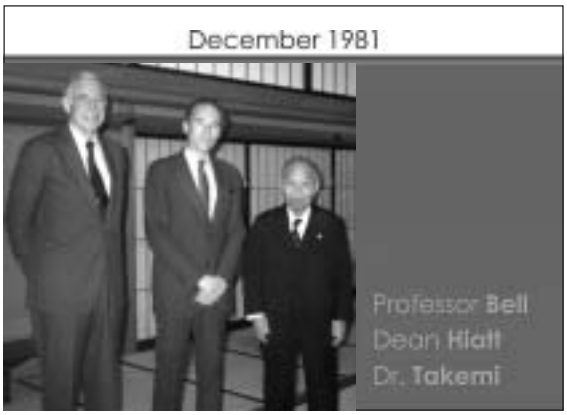
Origins

The Takemi Program emerged from the shared interests of Dr. Taro Takemi in Japan and Dr. Howard Hiatt in the United States. Each had long been concerned about the problems of promoting health and preventing disease, both in industrialized nations confronted by rising health costs and in developing countries burdened by persistent poverty. Dr. Takemi, as President of the Japan Medical Association, emphasized the need to bring together experts from medicine, public health, economics, law, politics, and other fields to find effective and equitable solutions to the development and distribution of health care resources. Dr. Hiatt, as Dean of the Harvard School of Public Health, similarly stressed the development of interdisciplinary approaches to the study of health problems and health policy.

In 1981, Dr. Takemi invited Dean Hiatt to Tokyo to address a meeting of the World Medical Association on the development and allocation of medical care resources. While there, they discussed the problems of international health. Out of their discussions grew the idea of the Takemi Program in International Health at Harvard. The Program was established in 1983, with initial funds donated by two private companies in Japan, and was named after Dr. Taro Takemi. The Program would seek to carry forward the central vision of Dr. Takemi that people from many disciplines must be brought together if better health is to be promoted in all countries, both rich and poor.[2]

Dr. Takemi and Dean Hiatt agreed that the Program would concentrate on the problems of mobilizing, allocating, and managing scarce resources to improve health, and of designing effective strategies for disease control and prevention and health promotion. Because of the severity of the health resource problems in poor countries, the Program would focus on these countries. To address these issues, each year the Program would bring together at Harvard a small group of Takemi Fellows, mid-career professionals from around the world, with an emphasis on participants from developing countries.

In September 1984, the first group of five Takemi Fellows arrived at the Harvard School of Public Health in Boston. Since then, twenty more groups have participated in the Takemi Program (through 2004–05), with a total of 175 Takemi Fellows from 48 countries, from Thailand to Kyrgyzstan, from The Gambia to Colombia. The geographic distribution of Takemi Fellows is shown by region in Table 1, along with a list of countries of origin. Takemi Fellows have included 31 from Japan, 23 from India, and 16 from Nigeria. Of all Takemi Fellows to date, 114



are from developing countries. This means that out of 144 Fellows from countries other than Japan, almost 80% are from developing countries.

The international network of Takemi Fellows since 1984 now includes prominent individuals in universities, private and government research institutes, ministries of health, nongovernmental organizations, and international agencies—spread in countries all around the world. The specialties of Takemi Fellows who have participated in the Program include economics, nutrition, nursing, health education, community health, epidemiology, bioethics, health services utilization, infectious disease, sociology, emergency medicine, health insurance, occupational health, political science, and others.

Tragically, Dr. Takemi died in Tokyo in December 1983, before he could meet any of the Takemi Fellows or guide the Program in charting its course. Since 1994, the Takemi Program has maintained a continuing collaboration with the Japan Medical Association, as part of the JMA's international health activities and as a way to remember Dr.

Table 1 Takemi Fellows Geographical Distribution

Geographical Distribution of Takemi Fellows 1984–2005: Totals by Region

Since its inception in 1984, the Takemi Program has had 175 Fellows from 48 countries, including the group of 2004–2005 Takemi Fellows.

East Asia	**54**	**Middle East**	**6**
Japan	31	Israel	3
China	11	Egypt	1
Korea	6	Turkey	1
Taiwan	6	Iran	1
South Asia	**31**	**Eastern Europe**	**4**
India	23	Poland	1
Sri Lanka	3	Russia	1
Indonesia	3	Azerbaijan	1
Pakistan	2	Kyrgyzstan	1
South East Asia	**9**	**Europe**	**9**
Thailand	4	France	3
Philippines	3	Denmark	1
Malaysia	1	Italy	1
Vietnam	1	Sweden	1
		Switzerland	1
Africa	**43**	The Netherlands	1
Nigeria	16	United Kingdom	1
South Africa	8		
Tanzania	3	**North America**	**7**
Ghana	2	USA	7
Kenya	2		
Uganda	2	**Latin America**	**12**
Burkina Faso	1	Brazil	7
Cameroon	1	Colombia	3
The Gambia	1	Mexico	1
Lesotho	1	Nicaragua	1
Malawi	1		
Morocco	1		
Sierra Leone	1		
Sudan	1		
Zaire	1		
Zambia	1	**Total: 175**	

Takemi's philosophy and ideas on health and medicine. Over the years since it began, the Program has been guided by a set of ideas about the concept and practice of international health. These guiding ideas are stated below in the form of seven principles that have emerged at the core of the Program.

Principles

Research emphasis

Perhaps the foremost principle of the Takemi Program's concept and practice of international health is that seeking new knowledge through research is essential to health improvement. Each Fellow is expected to carry out a research project, based on data collected before arrival at Harvard and using the university's resources available through faculty members, libraries, and computer facilities. Many mid-career professionals lack adequate time in their work at home to analyze data, read journals, and write papers for publication. The Takemi Program provides its participants with "protected time" —away from the administrative, teaching, and other obligations at home—and with access to high-quality resources, in people, books, and courses. Each Fellow is expected to produce at least one research paper of publishable quality on a topic of major importance to health policy.

Among the research papers completed by Takemi Fellows during the last two years are the following topics: understanding health inequity in the decentralized health system of Kerala State, India; the evolution of tobacco control in Japan and lessons from American experience; modified directly observed therapy system (M-DOTS) for HIV/AIDS patients in Colombia; and the policy context of medical-aid policy in Korea. Many of the Program's research papers (numbers 88 through 214) are available on the Takemi website, which was designed and implemented by a Takemi Fellow, Bodavala Ranganayakulu from India, who now heads an innovative non-governmental organization for rural development, called Thrive (see www.thethrive.org).[3]

The principle here is that Takemi Fellows are sharpening their research skills to participate in the world-wide health research system by adding to national and global knowledge on how to allocate resources better, in various countries and on different substantive problems. Some of the research papers use highly sophisticated statistical analysis to uncover unanticipated patterns of association in field data. Other papers employ epidemiologic or demographic modeling techniques learned at Harvard and applied to data sets from home countries. Some papers use policy analysis techniques based on economics, others based on political science. Each of the Takemi Research Papers (now well over 200 research papers) is itself a contribution to the essential research needed in every country to assess the nature of health problems and the effectiveness of proposed solutions, as advocated by the International Commission on Health Research for Development,[4] and each of the Fellows, as a result of his or her year in the Program, is better qualified to conduct research in the future.

Policy-oriented

A second principle is that the Takemi Program is aimed at producing research that assists in the design, implementation, and evaluation of health policy. From its start, the Takemi Program has concentrated on areas where not much support has gone: the study of health problems from the perspective of policy makers (rather than laboratory research). Individual Fellows, for example, have carried out epidemiological analyses that seek to explain the contours of specific diseases (such as research on tobacco-related cancers in India, conducted by a Takemi Fellow in 1984–85)[5] or economic analyses that show the cost-effectiveness of implementing certain programs (such as an assessment of the strengths and weaknesses of home-based care for HIV/AIDS patients in Uganda, by

a Takemi Fellow in 2002–03).[6] In presenting their research plans and analyses, Takemi Fellows are pushed by their colleagues and advisors to specify the policy implications of their projects.

Takemi Fellows are encouraged to bring their research results to policy makers in the United States, international organizations, and in their home countries, and to seek changes based on their research results. One Takemi Fellow in the first group (TF 1984–85), Prakash Gupta, testified before scientific commissions in the United States on the health implications of smokeless tobacco; another, Chinyelu Okafor (TF 1988–89), advised private foundations on the design of programs for improving maternal health in Africa and then helped implement the plans.[7] A third, Boniface Nwakoby (TF 1989–90), had the opportunity to present his research findings directly to his Minister of Health, Professor O Ransome-Kuti, in a seminar during the latter's visit to the Takemi Program. Several Takemi Fellows (from Belgium, Denmark, India, and Switzerland) have assumed key policy positions at the World Health Organization; and one Takemi Fellow (from Uganda) holds a senior position at the Global Fund to Fight AIDS, Tuberculosis and Malaria. Many Fellows work with international organizations and bilateral aid agencies in their home countries, in the design and implementation of health programs and policies.

In addition, the Takemi Program has collaborated with various Japanese and international agencies in organizing a series of major international meetings (the Takemi Symposium on International Health) on important health policy issues. These symposia have been attended by leading experts concerned with issues of international health, from universities, international agencies, and government ministries. The international meetings lead to published volumes, which include papers by Takemi Fellows. The books so far have addressed issues of: the conceptual bases for health policy in the 21st century;[8] policy responses to health, nutrition, and economic crises in the Third World;[9] the prospects and problems of international cooperation for health;[10] and working populations and occupational health in the Third World.[11] The most recent Takemi Symposium, held in 2000, was organized in collaboration with the Japan Medical Association on ethical issues in health and development.[12]

Interdisciplinary perspective

The Takemi Program is firmly based on one of Dr. Takemi's main principles: that interdisciplinary study is necessary if health problems are to be analyzed correctly. Each year of Takemi Fellows includes individuals with an array of disciplinary backgrounds, as noted above, including economics, epidemiology, community health, nutrition, biostatistics, social sciences, and clinical medicine. The Program is based on the conviction that research in public health policy requires a solid disciplinary foundation, but also a broader contextual understanding of the social environment within which health problems arise. Many preventive and therapeutic measures require changes in attitudes and behavior in order to improve health conditions. A narrow disciplinary focus may produce the correct technocratic answer, but one that is impossible to carry out, due to cultural, economic, or social factors.

In this sense, the Takemi Program advocates not only the application of epidemiology and economics to the analysis of public health problems, but also other social sciences—anthropology, sociology, political science, and ethics. Palitha Abeykoon (TF 1989–90) examined the experiences of several South Asian countries in health manpower policies to identify those factors of policy design that promoted effective implementation.[13] A paper by Akihiro Seita (TF 2003–04) looked at the Japanese experience of integrating tuberculosis into the primary health system and how this could be applied in other countries.[14] Another research paper,

by Allan Schapira (TF 1987–88), was written in the form of a teaching case module on how health care systems confront and manage the issues of chloroquine-resistant malaria in Africa.[15]

The Program promotes an interdisciplinary perspective through several mechanisms. By accepting individuals with strong disciplinary training, the Program creates a group with expertise in various fields. Then, the Fellows are placed in closely shared office space, encouraging informal interactions, so that one's discipline rubs off on one's neighbors. The weekly research seminar covers a range of disciplines in order to broaden the intellectual horizons of individual Fellows. Finally, the Program recommends that Fellows audit courses in their own disciplines and beyond.

Mutual respect

A fourth principle that underlies international health as understood in the Takemi Program is a non-hierarchical relationship of mutual respect among Takemi Fellows and also between Fellows and faculty members, with an emphasis on collegiality and equality. As mid-career health professionals who have advanced careers in research, service, and education and who are selected from an international competition, Takemi Fellows occupy a position of prestige within the Harvard community. Many Fellows lecture on their research and other topics in courses and seminars at Harvard University and other institutions. The Fellows enrich the educational environment at the School of Public Health, through their experiences and their expertise in particular fields. The Fellows also enrich each other's lives; their shared existence opens their minds to new ideas and perspectives. From personal friendships, Fellows gain international understanding. They come to appreciate basic similarities in health problems and policies as well as national differences.

A Takemi Fellow's relationship with the Faculty Advisor critically affects the quality of the fellowship and the research. The Program assures that the research relationship is based on mutual respect. Most Takemi Fellows carry out their research and complete the analysis and writing on their own. In some cases, faculty members contribute sufficiently to the research paper to be recognized as coauthors, but the Takemi Fellow is typically first author in the published version. The principle of mutual respect recognizes the existence of different skills between Fellows and advisors and also among Fellows; the principle also reflects the objective of promoting the intellectual development of advisors as well as Fellows. After the Takemi year, Fellows are encouraged to continue their relationships with Harvard faculty members and other researchers met at Harvard, all on the basis of mutual respect as colleagues.

Individual freedom

Along with the principle of mutual respect is the principle of individual freedom for Takemi Fellows. The Program imposes only minimal requirements on Fellows: to attend one group seminar each week, to join in an informal luncheon each week, and to produce a high quality research paper by the close of the academic year. Beyond that, Fellows are free to act as they please: to audit courses throughout the University; to sit in the library and read; to stay at home and write; to consult their advisor regularly or to ignore the advisor resolutely. Each Fellow is encouraged to use the rich resources of Harvard to achieve his or her individual research objectives, and the Program assists the Fellow in navigating the University's resource map.

The principle of individual freedom is based on the assumption that each Fellow knows what he or she best needs or wants at this critical midpoint in one's career. The array of activities is minimally structured, to allow each Fellow to chose the most appropriate particular blend. Similarly, the Program's weekly seminar does not seek to

impose a specific doctrine of health policy, but rather exposes the group of Fellows to a panoply of researchers, some already eminent and some still emerging, and all grappling with serious questions of resource allocation in health. In the words of one Fellow, the Program provides "a privileged moment for learning."[16] This freedom for Takemi Fellows represents a social good, intended to be used in the Program's overall mission of improving health conditions on a global scale. Fellows accept the freedom in exchange for an implicit acceptance of responsibility in advancing the Program's mission.

Community spirit

The community of Fellows, while at Harvard and thereafter, represents the sixth key principle for the Takemi Program. Each year, the Program seeks to create a community out of the group of Fellows, to bridge the cultural and intellectual boundaries created by geographic, disciplinary, and language differences. The Fellows share offices in close proximity, and the Program sponsors informal social occasions for both Fellows and families. By mid-year, the community has gelled to the point where Fellows strong in particular disciplines—often statistics and economics—are helping others in new skills, a form of TC/TF or Technical Cooperation among Takemi Fellows. The candid critique of research proposals and draft papers depends on a sense of communal trust and confidence, which is created through the weekly research seminars and luncheons and through the informal interactions among Fellows. The Fellows experience this community spirit, with its mutual support and exchange, as a positive outcome of the Program.

Promoting the broader community of Fellows, across different years, is accomplished through international meetings held every two or more years and through networking activities. In countries with more than one Takemi Fellow, the individuals meet on both a professional and social basis. These linkages have evolved into productive collaborations, as the number of Fellows has reached a critical mass. In the current year of Takemi Fellows (2004–05), Jui-Fen Rachel Lu, Associate Professor in the Department of Health Care Management, Chang Gung University, Taiwan, is doing research on the equity implications of the health care system in Taiwan. For this work, she is collaborating with other Takemi Fellows who are working on issues of equity. In addition, a number of Fellows, after returning home, have continued to work with Harvard faculty members on various projects related to health policy. How to harness the potential of the network of Takemi Fellows remains a key question for both Fellows and the Program. At the same time, this question reflects the Fellows' recognition that they have gained a long-term relationship with an international network.

Individual capacity building

The final principle of the Takemi Program emphasizes the importance of individual capacity building as an instrument for strengthening institutions and improving health conditions in developing countries. Enhancing the skills and experiences of individuals with leadership qualities is expected to contribute, both directly and indirectly (through research, teaching, and administrative positions), to the effectiveness of the institutions in which the individuals work. While more than one Takemi Fellow has been accepted from several institutions (including one in Nigeria, one in Japan, and one in China), the Program does not have a strategy of institution strengthening, as adopted by some foundations and international agencies. The emphasis on individuals rather than institutions resulted in part from limited resources within the Program, and also from a strategic choice at the Program's start. A number of these individuals, however, have emerged as leaders of national institutions, including: Bong-min Yang, who

is Dean of the Seoul National University School of Public Health in Korea; Max Price, who is Dean of Health Sciences at University of Witwatersrand in South Africa; Yin Li, who is the leading health policy analyst in China's State Council; and Friday Okonofua, who is Dean of the School of Medicine at the University of Benin in Nigeria and recently appointed as Executive Director of the International Federation of Obstetrics and Gynaecology (FIGO). In Japan many Takemi Fellows of the past two decades now occupy leadership positions in international health and public health, with Professor Uehara Naruo at Tohoku University, Professor Marui Eiji at Juntendo Medical School, Professor Nakamura Yasuhide at Osaka University, Professor Kobayashi Yasuki at Tokyo University School of Medicine, and Dr. Tanaka Keiji as Assistant Minister for Technical Affairs in the Ministry of Health, Labor and Welfare.

To date, most Takemi Fellows have returned to their home institutions, although some subsequently have changed positions due to severe political instability or evolving career objectives. The choice of mid-career professionals as Takemi Fellows increases the likelihood that individuals will return to their institutional positions at home. But the Program has no written or legal requirement on returning; it is rather an implicit expectation. At the same time, the Program recognizes that in some cases, individual development may depend on not returning.

Implications

The past problems of international health, as a field, are well known. These problems include a tendency toward one-way imposition of Western values and ideas on developing country people and organizations,[17] the creation of dependency and the distortion of local priorities through foreign aid,[18] and the intermingling of military, mercantile, and missionary objectives with health improvement goals.[1] As Ines Perin (TF 2000–01) wrote in her research paper: Who is helping whom in international health, and based on what sort of ideas and motives?[19] What are the ethically acceptable motives for activities in international health?

The seven principles embodied in the Takemi Program offer some directions for the future of international health. These principles, however, are not comprehensive, leaving out among other things biological research and institutional capacity-building. But the principles provide a good beginning.

In proposing this process of redefinition, it is important to recognize that the Takemi Program is now confronting several issues related to the broader concept and practice of international health. First, the Takemi Program has focused its activities on developing country problems overseas, while paying relatively little attention to similar problems in our backyard in Boston. A growing movement in the United States is seeking to bring the lessons of international health back home, emphasizing the commonalities in problems and solutions for improving health problems in both rich and poor societies.[20] The Takemi Program may need to address these commonalities more directly and effectively.

The Program is also confronting the long-term sustainability of its activities. While the Takemi Program initially received full financial support from Japan, now only core administrative costs are covered by contributions from Japan, through annual contributions from the Japan Pharmaceutical Manufacturers Association, plus support for Japanese Fellows from the Japan Medical Association. All other Fellows must seek external financial support. The Carnegie Corporation of New York for a decade in the 1990s provided generous support for Takemi Fellows from sub-Saharan Africa, because the health needs are so great in that part of the world. The Merck Company Foundation provided generous grant support for Fellows each year, for the past decade. Through these contributions, the Program has been able to

provide financial support for a few applicants, but most Fellows must raise their own funds or are financed by an external grant from a funding agency or private foundation. Each year, these financial constraints prevent the participation of some exceptional applicants.

As part of the Program, each Takemi Fellow produces at least one research paper. Many of these papers have been published in books or international journals, reflecting the Program's efforts to assure a wide dissemination of the research findings. A number of the research papers by Takemi Fellows have had significant impacts on national and international health policies.

To gain a qualitative evaluation of the Program's activities, past Takemi Fellows were surveyed in 1990. The responses demonstrated that the Program is fulfilling its objectives in several important ways: providing participants with access to research resources; exposing participants to new analytic approaches and concepts in their own and other disciplines; creating a supportive environment for research and writing; and establishing international linkages that can continue in future research activities. The survey indicated that the Program could be providing more follow-up support for Fellows once they return home, but it also revealed satisfaction among past participants with the Program's role as a catalyst for promoting and improving research and as a community for bringing together diverse disciplines and nationalities.

From a broader perspective, the Takemi Program illustrates two important patterns in international cooperation for health. First, the Program demonstrates that international cooperation can effectively contribute to improve developing country social conditions through the promotion of research and individual researchers from those countries. A challenge for the coming decades is to find mechanisms to harness additional resources (from the United States, Japan, and elsewhere) in ways that help improve health conditions in poor countries. Second, the Program illustrates that universities in rich countries have an important role to play in international health—as long as these institutions remain intellectually alive, responsive, demanding, and at the cutting edge of research. The challenge is to find the resources to make these university resources available to researchers in developing countries, as the Takemi Program has sought to achieve.

In conclusion, I hope that the Takemi Program will continue to contribute to the efforts to create a new international health. Such efforts, I believe, could contribute to a more truly international concept and practice of international health.

Acknowledgements

The author appreciates the insightful comments received from past Takemi Fellows, Dr. Christopher Wood, and the late Professor David E Bell, Acting Director of the Takemi Program in its initial years. The assistance of Dr. Marc Mitchell (Faculty Advisor for the Program) and Ms. Catherine Haskell in commenting on this paper and assuring the Program's continuity is greatly appreciated.

References

1. Gómez-Dantés O, Khoshnood B. Evolution of international health in the twentieth century. Salud Pública Méx. 1991;33: 314–329.
2. Hiatt HH. The conceptual contributions of Dr. Taro Takemi to the Takemi Program in International Health. In: Reich MR ed. Health Policy Toward the 21st Century: Health Problems Beyond the National Boundary. Boston, MA: Harvard School of Public Health; 1985:16–21.
3. Takemi Program in International Health, Harvard School of Public Health, see: http://www.hsph.harvard.edu/takemi.
4. Commission on Health Research for Development. Health Research: Essential Link to Equity in Development. New York, NY: Oxford University Press; 1990.
5. Gupta PC, Aghi MB, Bhonsle RB, et al. An intervention study of tobacco chewing and smoking habits for primary prevention of oral cancer among 12,212 Indian villagers. In: Zaridze DG, Peto T eds. Tobacco: A Major International Health Hazard (IARC Scientific Publications No. 74). Lyon: International Agency for Research on Cancer; 1986.
6. Walker M. An assessment of home-based care programs in

Uganda: their strengths and weaknesses. Takemi Research Paper No. 213. Boston, MA: Takemi Program in International Health, Harvard School of Public Health; June 2003.
7. Okafor C, Olukoya AA. Women's Perspectives on Maternal Mortality and Morbidity: Safe Motherhood Nigeria 1990. New York: Family Care International; 1990.
8. Reich MR ed. Health Policy Toward the 21st Century: Health Problems Beyond the National Boundary. Boston, MA: Harvard School of Public Health; 1985.
9. Bell DE, Reich MR eds. Health, Nutrition, and Economic Crises: Approaches to Policy in the Third World. Dover, MA: Auburn House; 1988.
10. Reich MR, Marui E eds. International Cooperation for Health: Problems, Prospects, and Priorities. Dover, MA: Auburn House; 1989.
11. Reich MR, Okubo T eds. Working Populations and Health: Strategies for the Third World. Westport, CT: Greenwood Press; 1990.
12. Harvard SPH Takemi Symposium. International Health and Medical Ethics in the 21st Century. Tokyo: Japan Medical Association; December 1–2, 2000.
13. Abeykoon P. Geographical balance of health manpower: policy experiences of some South East Asian countries. Takemi Research Paper No. 44. Boston: Takemi Program in International Health; 1990.
14. Seita A. Think PHC, do TB. Japan's experience in scaling up tuberculosis control and health system. Takemi Research Paper No. 217. Boston, MA: Takemi Program in International Health; June, 2004.
15. Schapira A. Policies for resistant malaria and the health care system: a course module. Takemi Research Paper No. 30. Boston, MA: Takemi Program in International Health; 1988.
16. Rainhorn JD. Personal communication. March 7, 1991.
17. Taylor CE. Changing patterns in international health: motivation and relationships. Amer J Pub Hlth. 1979;69:803–808.
18. Muhondwa EPY. The role and impact of foreign aid in Tanzania's health development. In: Reich MR, Marui E eds. International Cooperation for Health: Problems, Prospects, and Priorities. Dover, MA: Auburn House; 1989:173–206.
19. Perin I, Attaran A. Trading ideology for dialogue: an opportunity to fix international aid for health? Lancet. 2003;361:1216–1219.
20. Morgan R. Bringing the lessons of international health back home. Takemi Discussion Paper. Boston: Takemi Program in International Health; 1991.

Medical Care Advancing with Society

JMAJ 48(5): 256–263, 2005

Akira Teraoka*1

Key words Medical care, Society, Informed consent, Access to medical records, Quality of care, Patient safety

Introduction[1,2]

In the last few decades, there has been remarkable progress on the medical front. Especially, medical technologies in fields such as aging and dementia, cancer, infectious diseases, organ transplantation, and gene therapy, all of which are such debating issues to the general public as well as medical care providers, have dramatically advanced not only from scientific perspective, but also in terms of broadening the window of opportunities on numerous treatment choices. Accordingly, medical care professionals have more options in assisting the patient's decision-making process for medical treatments than decades ago. However, if medical care professionals don't provide patients with medical treatments in such ways that meet demands of both patients and of society, no matter how heroic they may seem, those medical treatments fall through as medical "care" since they are not able to achieve the core purpose of medicine; they lack functions to serve both individual and public health. It is worth mentioning medical care loses its social values unless it serves what is in the best interests of patients and society as well. That is, only when medical expertise and technologies are applied in situations where both people and society can play roles, does medical science have its social values in the most effective way.

With the theme "Medical Care Advancing with Society", this paper will examine whether the medical care services delivered by medical practitioners in Japan over the past decades have adequately responded to the demands of our society, and then, will clarify which aspects of medical care services have turned out successful and which have ended up otherwise. In doing so, the paper will identify several problems that have been under scrutiny in recent medical practice of this country, and will also raise a question; how should Japanese medical practitioners do to enhance their abilities to meet the demands of society? Furthermore, it is my hope to lay out several suggestions on what to be done to improve quality of medical care to better serve not only individual patients, but also society as a whole.

Changes in the Medical Care Delivery System[3]

Medical practice is the communication between physicians and patients and begins when a patient first pays a visit to a physician. Medical services start to be delivered at this point, the delivery of medical care services

*1 Japan Medical Association, Tokyo
Correspondence to: Akira Teraoka MD, Vice President, Japan Medical Association, 2-28-16, Honkomagome, Bunkyo-ku, Tokyo 113-8621, Japan. Tel: 81-3-3946-2121, Fax: 81-3-3946-6295, E-mail: jmaintl@po.med.or.jp

being undertaken within a given framework and according to established rules.

Under the universal medical care insurance system in Japan, enacted into law in 1961, the entire population is covered by some form of medical insurance, guaranteeing every citizen equal rights to receive medical attention at any time and at any medical facility. With its fundamental theory and with the Medical Service Law, that states "based on the principles of the respect for human life and individual dignity and the bond of trust between the provider and the recipient, medical care must be provided in such ways that are consistent with the patient's physical and mental condition", and stipulates the basic rules for the delivery of medical services as well the medical care delivery system holds a substantive position within society.

The medical care delivery system is not immutable, but has changed in response to the needs of society in successive generations. A brief trace of these changes reveals that the Medical Service Law enacted in 1948, in our country that had been devastated by the war, was focused on the provision of care to patients with infectious and other acute diseases; there were few medical facilities at the time and quantitative development was identified as an urgent undertaking.

Some thirty years after the end of the war, medical facilities had been developed around the country and Japan had essentially achieved its quantitative goals. However, problems with the uneven distribution of medical resources among the regions came under scrutiny resulting in the first amendment of the Medical Service Law in 1985, which introduced the Medical Care Plan. According to Ministry of Health, Labour and Welfare of Japan, the Medical Care Plan aimed at the promotion of systematic development of high quality health care in local communities by effectively utilizing medical resources and distributing the resources adequately while establishing the network and functional assignments among medical care related facilities. More specifically, multiple numbers of secondary medical regions were assigned for general hospital beds within each district of the prefecture, and "the required number of hospital beds" was set for each district to adequately distribute hospital beds. But from another viewpoint, the law has acted too much restrictive to activities of regional general hospitals resulting in gradual decrease in the total number of hospital beds.

Changes in all aspects of society and the pace at which they were occurring began accelerating around 1989, and there were calls for the efficient delivery of appropriate medical care in order to respond to the rapid progression of demographic aging and the resultant change of disease patterns. In response to these demands, the second amendment of the Medical Service Law was enacted in 1992. This redefined the conceptual standards of the medical care delivery system and established an institutional framework for special functioning hospitals and long-term medical care beds.

The need to respond to burgeoning numbers of people requiring nursing care and increasing demands for the provision of information in layman's terms led to the passing of the third amendment in 1997. This revision required physicians to provide patients with explanations of treatment being received and to obtain their understanding of the same, enabled clinics to set up the long-term medical care beds and established the regional medical care support system by introducing Regional Medical Care Support Hospital and by defining collaboration between medical facilities more clearly. The third amendment of the Medical Service Law was positioned as a Long-Term Care Insurance related bill in that it was intended to prepare more beds usable under the forthcoming Long-Term Care System.

The fourth amendment was passed in 2000, the goals of which were to promote further development of the system for providing inpatient care and the provision of

information in medical care. This amendment, moreover, made it mandatory for physicians to undertake at least two years of post-graduate clinical training with a view to improving the fundamental competence of physicians. The Long-Term Care Insurance system was also established in the same year, marking a genuine step forward in the integration of medical and nursing care and a word of English origin "ケア kea" that means care has come to be recognized as a medical term.

As this demonstrates, the medical care delivery system has undergone major modification over the years in response to both changes in the environment surrounding the system and the diversifying needs of Japan's citizens. During this time, the variety of services available to local residents have expanded and many medical, health and welfare service providers have become involved in the delivery of medical care.

In the context of this new environment it is critical that every local resident be able to have a "Personal Physician"—a doctor familiar to him or her who knows best the patient's condition inside out. This not only allows essentially all patients to receive optimal treatment, but also to seek counsel without hesitation, advice on the care most suited to their needs and, where necessary, referrals to specialist hospitals or physicians.

The term "Personal Physician" is from the patient's perspective. The Japan Medical Association (JMA) is actively promoting improvements in the roles of these "Personal Physicians".

As stated above, medical practitioners are required to adopt a broad-based approach that covers all aspects of medical care, from emergency care to end-of-life treatment, while focusing on both the needs of patients and the demands of society. They must deliver highly transparent, high quality services that are both safe and reassuring to patients. Additionally, the increasingly intense focus on lifestyle-related diseases makes it paramount that a great deal of energy be now expended on preventive care to ensure a better quality of life for the citizens of Japan.

Advances in Medical Science and Patients' Needs

It is clear that advances in medical science have had a significant impact on what is available to medical treatment today. When a new medical technology with possible high recovery rates is developed, patients naturally hope to enjoy its benefits. They wish to collect detailed information on the treatment and to explore its merits by comparing to conventional treatment methods. This active behavior or hope on the patient's side has a great impact on how physicians provide medical information for patients, which affects the patient's medical decision-making process and eventually treatment process as well. When patients receive medical care, concern towards this new intervention varies depending on each patient. In general, most patients seem to have strong interest in diagnostic examinations and surgical procedures. Many patients are undoubtedly interested in and have high hopes for surgical procedures with less physical invasion and psychological stress. For example, patients tend to prefer endoscopic procedures to laparotomy or thoracotomy that requires a shorter period of hospitalization. Unquestionably, a large number of people want to be examined by the newly invented methods if they are less invasive and more accurate and/or more informative than conventional ones.

Meanwhile, there has been so much attention paid to patients' own life values or philosophies towards how they want to be treated during the process. These individual wishes to control their own bodies with their own sets of values have raised such complicated questions revolving around end-of-life issues such as "How long does the patient want life-sustaining treatment continued?" or "When does the patient want

the treatment discontinued?"

In this modern world, interest in cutting edge medical technologies, including gene therapy and genetic screening, is on the enormous rise more than ever. If these technologies make it possible to accurately identify a predisposition to a specific disease or reactions to specific drugs—things that could not be detected using earlier medical technologies—and allow patients to receive sophisticated treatments or preventive medical care, there is no doubt that the new technologies would draw so much attention from both patients and society as a whole as well. The idea that genetic research could lead to the development of ice-breaking therapies obviously brings hope to those suffering from intractable diseases for which there are no effective treatments available at present. Moreover, the recent development of assisted reproduction technologies (ART) will bring the new hope for those couple who desperately want to conceive children.

As was described above, it is worth noting that dramatic changes and progress in medical science have happened in response to diverse needs and demands from both individual and society. Considering how closely needs of patients and society are intertwined with medical progress, physicians, whether or not they are personally capable of performing the procedures, need to maintain their studies on a daily basis, keep themselves updated with new researches, and cultivate their thinking so that they can provide the latest knowledge and information on new medical techniques for patients. At the same time, with the advent of cutting-edge treatments such as gene therapy and ART, medical practitioners should give more consideration to issues around medical ethics at both individual and community level. We also should make efforts to generate public awareness on medical ethics so people can be more sensitive to such issues from perspectives of patients who receive medical treatments.

Furthermore, there has been much debate on the use of the various electronic information and telecommunications technologies (IT) in medical practice recently. As physicians we need to approach this issue both sensibly and flexibly. As long as IT is handled by humans, there is always room for human error, and also there might be some complicated information that machines alone can't deal with. That is, IT is not always perfect. In consideration of these possible problems that could be caused by introduction of IT, we have to take special cautions so that IT can be utilized only in a way medical practitioners use it as mere assistance, not in a way they entirely depend on it with information processing. This kind of extra caution taken by physicians will lead to improvement of quality of care and contribute to patients' safety and benefits.

The Physician-Patient Relationship

As has been pointed out above, advances in medical science have multiple effects on what is available to medical treatment today. It would be no exaggeration to say that physicians' capability to provide the good care depends on whether they can fully understand patients' needs and have trustworthy relationships with patients. In the past, communication between physician and patient was commonly paternalistic in our country too, that is "placed him or herself in the hands of a physician or a medical institution wholeheartedly". However, in recent years, this relationship has evolved into shared decision making between equals.

The following paragraphs explore this type of physician-patient relationship on the ground (i.e., in the places where treatment is provided) from three separate perspectives: the active provision of information to patients; protecting patient rights and benefits, especially confidentiality; and achieving the patient safety.

There can be no objection to the fact that what is termed informed consent—a process involving the provision of intelligible

explanations on a patient's current condition, the treatment that is to be undertaken and the results expected therefrom, together with information on the track record of the diagnosing physician or the medical institution at which the treatment is to be provided, and gaining their consent based on sufficient understanding and acceptance of this information—is fast becoming standard practice. Stemming from global abhorrence of the atrocious human experiments performed during the Second World War, the concept of informed consent was upheld by the World Medical Association in the Declaration of Helsinki adopted in 1964 as an ethical principle to be upheld by physicians and researchers, resulting in the spread of laboratory protocol, predominantly in Europe and the United States of America. Today, informed consent has also become critical to advancing medical care in Japan.

(1) The provision of information to patients

(i) JMA efforts in respect of informed consent

In 1990, the JMA Bioethics Council issued the Report on Explanations and Consent. This was followed, in 1995, by the publication of a report by the Study Commission on Informed Consent of the Ministry of Health and Welfare (as was) emphasizing the importance of informed consent in routine medical practice. The inclusion of a clause making efforts on "explanation and understanding" obligatory in Article 1, Clause 4-2 of the Medical Service Law in 1997, demonstrates that informed consent has come to occupy an unassailable position as a component of medical practice.

However, an examination of individual cases reveals that as to matters such as the qualifications and experience of physicians, the situations of individual patients and their capacity to understand the explanations given to them, and the fiduciary relationship between physician and patient, there remains considerable disparity among the state of practicing informed consent and there is considered to be much room for improvement in this respect. There is a need for fresh debate acknowledging the fact that medical care by nature is best conducted on the basis of trust and cooperation between patients and physicians.

(ii) The issue of access to medical records

The issue of access to medical records is significant in that it is central to the provision of information by medical practitioners. Having heard the explanation of their physician, patients who seek a more in-depth understanding of their treatment, or those who consider that they have not obtained sufficient information from the physician's explanation alone, will likely want to see the medical records or receive the copies.

This issue has been the subject of occasional debate over the years in Japan. In 1998, the "Council on the use of Medical Records" of the Ministry of Health and Welfare (as was) published a report containing the results from a thoroughgoing study on this matter. Though there was a high-profile split over whether access to medical records should be made mandatory under law or left up to the individual physicians, in its final report, the Council avoided making any emphatic statements on either side of the argument.

In 1999, the JMA has established the "Policy on the provision of medical information" as a voluntary ethical code that obliges members to respond to requests for access to or making copies of their medical and/or examination records. This policy was subsequently revised in 2002, with the addition of a provision making it obligatory to respond to requests from relatives for access to medical records upon or after the death of the patient. Acting in accordance with the provisions of the JMA policy, national university hospitals, national hospitals, and other medical institutions and groups have

successively adopted similar policies on access to medical records, leading to the rapid spread of voluntary medical records disclosure on the medical care delivery side.

In September 2003, the Ministry of Health, Labour and Welfare notified all the medical facilities of its "Policy on the provision of medical information", the content of which is virtually identical to that of the JMA policy. This demonstrates that, without resorting to legislation, physicians' own efforts led by JMA to establish the practice of care receivers' side apt access to medical records in medical facilities are gradually bearing fruit. However, regrettably, there have been incidences of malpractice involving the falsification of medical records. In this respect, it would seem that the medical profession has not yet earned the trust of society.

(2) Protecting patient rights and benefits

(i) Second opinions

For patients confronting major problems such as the prospect of undergoing surgery or receiving highly invasive examinations or treatment on the recommendation of their primary-care physician, it is quite natural that the problem cause serious concerns. For example, is surgery really necessary? Or are other, better alternative treatments available?

In such cases, the patient can request the opinion of another physician. Considering these natural requests, allowing patients to get a "second opinion" is a reasonable stance for physicians to adopt and physicians should really guarantee patients who do not have sufficient medical knowledge this opportunity. Asking for second opinions involves requesting another physician to make a decision based on the judgment of the primary-care physician, or on information detailing the grounds for that decision. It is therefore critical that the original medical information should be provided accurately and sufficiently. Accordingly, this calls for the same positive attitude toward the provision of medical data referred to above.

Candidly speaking, second opinions have yet to become sufficiently pervasive in Japan. However, in view of the direction in which medical advances are heading, or to put it another way, the fact that the treatment options open to patients will continue to expand as medical science advances, medical practitioners in this country need to reaffirm the importance of establishing the system of second opinions.

(ii) Protecting personal information on patients

Personal Information Protection Laws were enacted in May 2003 and are to be put into enforcement from April 2005. The laws are specifically targeted at organizations handling large volumes of personal information and oblige them to manage that information appropriately; they are therefore applicable to all industries. The laws make the protection of personal privacy a statutory duty and are based on the fundamental principles that the collection, management or use of personal information of an individual in opposition to his or her wishes are not permitted. Further, to allow individuals to check the accuracy of information pertaining to them, the laws grant individuals the right to request the disclosure of their data and its correction. This concept is recognized throughout contemporary society and must be respected even more sensitively throughout the medical profession.

Understandably, the confidentiality of medical facilities and medical personnel is already written into criminal law and into the regulations of other professions involved in the provision of medical care, and efforts to promote the disclosure of medical records, such as the voluntary policy of the Japan Medical Association, have been taken from early on. The enforcement of the Personal Information Protection Laws represents an opportunity to take a fresh look at how

personal information should be managed sensitively and appropriately in all medical institutions.

As regards the handling of genetic data, a subject that is coming under increasingly close scrutiny, given the exceptionally broad scope of information can be expressed as genetic data, the entire medical profession needs to be conscious of the fact that this topic must be approached with particular discretion.

(3) Ensuring the quality of care and patient safety

Improving the quality of medical care and ensuring the safety of patients during diagnosis and treatment are the highest priority tasks imposed on physicians and the JMA, and must continue to be addressed in earnest. We must keep uppermost in our minds also the fact that the strongest demands on the medical profession from patients and the general public center around these two aspects of medical care.

It goes without saying that physicians and other medical service personnel have been zealous in tackling the issue of ensuring patient safety to date. However, media reports of cases of malpractice continue as the principal cause of public mistrust of the medical care system.

In 1997 the JMA had set up a "Medical Safety Policy Committee" as an internal organ that recommended the importance of fomenting an atmosphere that would enable any person involved in the medical act to speak up without reservation and be conducive to constructive discussion on accident prevention and measures needed to ensure safety, and initiated efforts to promote patient safety by awareness-raising campaign in hospitals. But, in spite of these efforts, a so-called "patient mix-up accident" occurred in 1999. Since then, the Medical Safety Policy Committee has been much more diligently undertaking a variety of other activities aimed at ensuring patient safety and preventing medical accidents.

During this period, the government has also implemented various measures, such as collecting incident reports. In October 2002, a measure was adopted targeting medical institutions with hospitalization facilities. Under this measure, points would be subtracted from treatment remuneration calculations at those institutions failing to apply prescribed medical safety measures. The JMA drew up a "Model Medical Safety Management Guideline" in August of that year, as a guide to introducing accident prevention measures for medical institutions. At all medical institutions, safety measures are currently being considered the proactive engagement in the process of delivering medical care services to ensure patient safety.

A major issue for the entire medical profession now is to initiate concrete efforts to develop and propagate measures aimed at preventing the recurrence of accidents and near-misses based on the collection and analysis of related data, with a view to producing results, that is prescribing effective measures that will link directly to the prevention of medical accidents. Towards this end, the JMA is strengthening its efforts in three areas: 1) improving the quality of physicians and other medical personnel; 2) ensuring the safety of facilities, drugs, and medical equipment; and 3) improving the quality of medical institutions as it relates to safety.

Today's society is being referred to as a risk society. Therefore, charged with the responsibility of ensuring the safety and peace of mind of people, just the medical profession must avoid generating anxiety within society at all costs.

Conclusion: Returning to the Basics of Medical Care

This paper has addressed a big issue of socially applied medicine. I emphasized that medical practitioners should fully understand patients' needs and also meet social demands.

They should deliver medical services not only for the patient but also in line with progress in society.

As modern medical science has advanced hand in hand with society, patients' needs towards medicine have diversified. This proves that medical progress has created the social environment where patients can express their own hopes and opinions clearly. It is very important that physicians should make more comfortable environments where patients can appeal to their own rights to take medical decision-making. At the same time, patients should also become more sensitive to issues around modern medical progress and make efforts to communicate with physicians. In other words, physicians and patients should work hand in hand to pursue better medicine.

Many aspects of the medical profession still remain to be reformed. Henceforth we must continue to be not only sensitive but also open-minded towards the opinions of patients and at the same time ensure that medical care continues to advance with society while harmonizing scientific medical progress with the social demands.

References

1. Teraoka A. Medical care changing with times. Currently Practical Neurosurgery. 1998;8(2):151–158. (in Japanese)
2. Takaku F ed. I no Genzai. Tokyo: Iwanami Shoten; 1999. (in Japanese)
3. Annual Reports on Health and Welfare, 1998–1999 Social Security and National Life. http://www.mhlw.go.jp/english/index.html.

Report on Retraining for Physicians Subject to Administrative Punishment

JMAJ 48(5): 264–266, 2005

Nobuya Hashimoto*1

Key words Administrative punishment, Medical license revocation, Suspension of medical practice, Ethical training, Technical training, Continuing medical education

Introduction

A Ministry of Health, Labor and Welfare panel on retraining for physicians subject to administrative punishment released its findings in a report on March 2005.

According to stipulations detailed in Article 7 of the Medical Practitioners Law, physicians subject to administrative punishment may either have their medical license revoked or be suspended from medical practice for a fixed period, usually between one month and five years.

In addition to professional negligence resulting in injury or death due to medical malpractice, the wide ranging grounds for issuing administrative punishment include violation of civil law based on the Medical Practitioners Law, violation of the Narcotics and Psychotropics Control Law, fraudulent claims for medical fees, violation of the Income Tax Law, bribery, fraud or theft and indecency.

As of March 2005, the number of physicians subject to administrative punishment over the 34 year period dating back to 1971 was 620, 47 of which had their medical licenses revoked and 573 were suspended from medical practice.

At present, physicians suspended from medical practice are able to recommence treatment of patients once their period of suspension has passed. It is this problem that sparked discussion concerning the need for retraining for such physicians.

There has been a surge in mistrust and anxiety regarding medical treatment in Japan in recent years due to the sheer volume of reports of medical malpractice around the country. This was one of the factors that led the Minister for Health, Labor and Welfare to launch an urgent appeal for measures to tackle medical malpractice, calling for investigation into retraining for physicians subject to administrative punishment, in December 2003. This resulted in the Medical Ethics Council Subcommittee on Medical Ethics establishing the aforementioned panel in March 2004. The panel met five times during the period from October 2004 to March 2005 to engage in intensive discussion. It consisted of one religious expert, one relative of a medical malpractice victim, two legal experts, one journalist, four medical professors, one legal

*1 Japan Medical Association, Tokyo
Correspondence to: Nobuya Hashimoto MD, PhD, Executive Board Member, Japan Medical Association, 2-28-16, Honkomagome, Bunkyo-ku, Tokyo 113-8621, Japan. Tel: 81-3-3946-2121, Fax: 81-3-3946-6295, E-mail: jmaintl@po.med.or.jp

professor, one general hospital director and one of the board members of the Japan Medical Association (JMA).

Details of Retraining

Retraining will be based on a two tier program consisting of ethical and technical training.

Based on the JMA's Basic Code of Professional Ethics (2004), programs of ethical training will include the likes of educational lectures, community service activities, physical and mental training, classes and reports are to be put together in line with the severity of the punishment issued and the circumstances of the relevant physician. Although the period of training will vary on a case-by-case basis, it will be in the region of three months to one year. During this period, physicians undergoing retraining will be assigned a preceptor, with whom they will have to meet roughly once a month, although the frequency of such meetings may also vary on a case-by-case basis.

The panel determined that the preceptors who will oversee physicians subject to administrative punishment will be called "advisory supervisors."

There are two key reasons for carrying out medical technical training. The first of these is, obviously, to give physicians who have been punished for errors in specific areas the necessary training in the relevant skills and technology. The second is that physicians who are issued a long period of punishment need retraining in medical skills and technology before returning to the medical practice.

Technical training will be conducted at specific medical institutions by designated expert physicians, to be determined based on the instructions of the relevant advisory supervisor. Although it is possible for advisory supervisors themselves to conduct technical training, this generally be delegated to a different medical expert in the case of any specialist skills or technology.

Retraining Assessment and Certification

Although assessment of retraining carried out in this way will be handled by advisory supervisors via assessment reports, certification upon completion of training will take the form of a report issued by the Ministry of Health, Labor and Welfare. In the event that technical training assessment indicates problems in the relevant areas, the physician will not be permitted to work unsupervised in such areas until he or she has acquired the required level of expertise (through appropriate training) to recommence medical practice.

Training for Advisory Supervisors

Those acting as advisory supervisors as part of the retraining of physicians subject to administrative punishment will have a major role to play and bear a great deal of responsibility. Therefore, training sessions will be held for advisory supervisors to ensure that all supervisors are equipped with the same essential skills. Training is currently envisioned for approximately 100 advisory supervisors, and the training program will include professional ethics for physicians, the essential qualities a physician should have, the medical care system, medical safety measures, curriculum planning for physicians subject to administrative punishment, and assessment methods. It is scheduled to last two to three days.

The Ministry of Health, Labor and Welfare is set to carry out trials of this system before the end of 2005, with the aim of revising the Medical Practitioners Law in the near future to make retraining mandatory for all physicians given administrative punishment.

The JMA is giving its full support to retraining for physicians and hopes to bring the concept of professional autonomy for

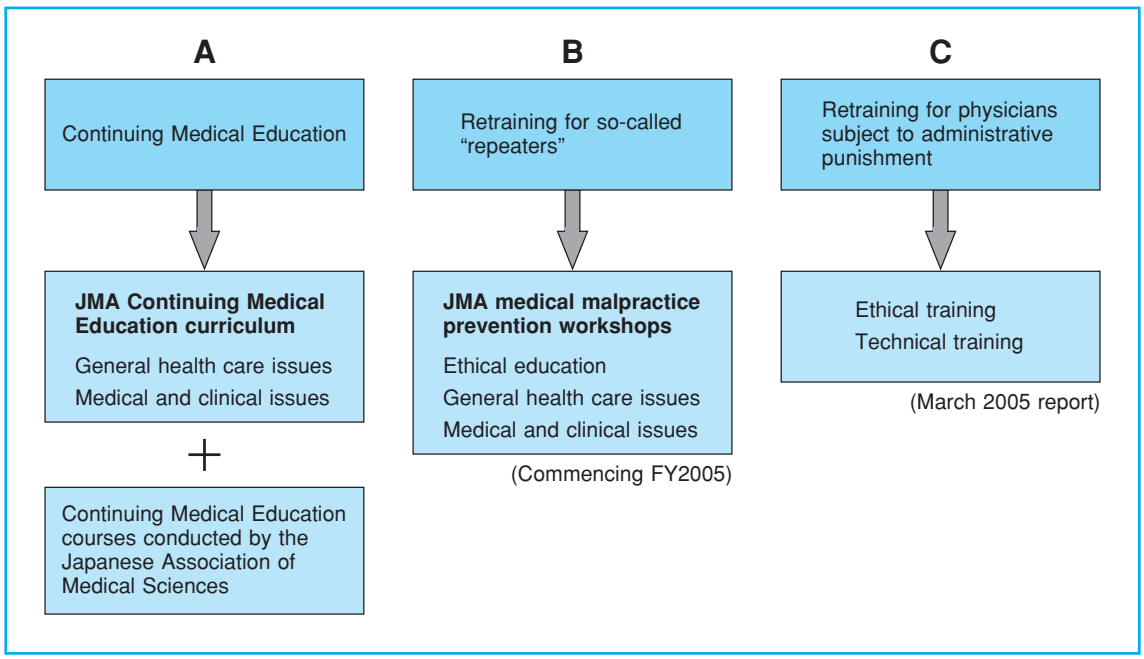


Fig. 1 Three categories of training for physicians after completion of clinical training

physicians to the forefront.

Three Categories of Training for Physicians

One final point of note is that retraining for physicians subject to administrative punishment should be thought of as something entirely separate to the standard form of continuing medical education for physicians. Training for physicians after graduation in medicine and completion of clinical training can be broadly divided into three categories (Fig. 1). Category A is standard continuing medical education, which is conducted as part of the activities of the JMA and medical associations on a regular basis.

Category C is retraining for physicians subject to administrative punishment, as discussed by the aforementioned panel.

Category B is a separate category for so-called "repeaters," that is physicians who have been the subject of medical disputes on repeated occasions. The JMA is currently looking into training for physicians in this category and is making the necessary preparations to commence training before the end of this year.