Table 1. Patient characteristics

Parameter	Value
No. of registered patients subjected to analysis	14,064
Mean age, years	66.8 ± 10.2
History of myocardial infarction, n (%)	2,003 (14)
Abnormal cardiothoracic ratio, n (%)	3,542 (25)
Hyperlipidemia, n (%)	11,684 (83)
TC, mg/dL	214.9 ± 36.5
TG, mg/dL	163.0 ± 119.3
HDL-C, mg/dL	55.2 ± 15.3
LDL-C, mg/dL	128.8 ± 32.7
Hypertension, n (%)	12,402 (88)
SBP, mmHg	142.6 ± 16.7
DBP, mmHg	80.1 ± 14.9
Diabetes mellitus, n (%)	7,166 (51)
Fasting blood glucose, mg/dL	121.2 ± 42.7
HbA1c,%	6.62 ± 1.48
Obesity [BMI, ≥25 kg/m^2], n (%)	5,839 (42)
BMI, kg/m^2	24.7 ± 3.5
Smoking, n (%)	2,087 (15)
Alcohol consumption, n (%)	4,756 (34)

TC, total cholesterol; TG, triglycerides; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol, SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index

Patient characteristics are shown in **Table 1**. They included 2,003 patients (14%) with a history of myocardial infarction, 11,684 (83%) with hyperlipidemia, 12,402 (88%) with hypertension, and 7,166 (51%) with diabetes mellitus. Those with multiple lifestyle diseases included 6,123 (44%) with hyperlipidemia and hypertension, 1,830 (13%) with diabetes mellitus and hypertension, and 1,130 (8%) with hyperlipidemia and diabetes mellitus. All 3 diseases were present in 4,131 (29%), and 1,828 (13%) also had obesity (defined as BMI ≥25 kg/m^2; **Fig. 1**).

Time-Course of Changes in Coronary Risk Factors

1) Obesity, Smoking, and Alcohol Consumption

Over the 3-year survey period, the percentage of patients with obesity remained at 43%; that of smokers decreased from 15% to 13%, and that of those drinking alcohol changed from 35% to 34%. Hence no major changes were observed overall.

The percentage of patients offered guidance to stop smoking for smokers and diet and exercise therapy for all registered patients showed no significant change over 3 years.

2) Lipids

Fig. 2 shows changes of mean LDL-C values and

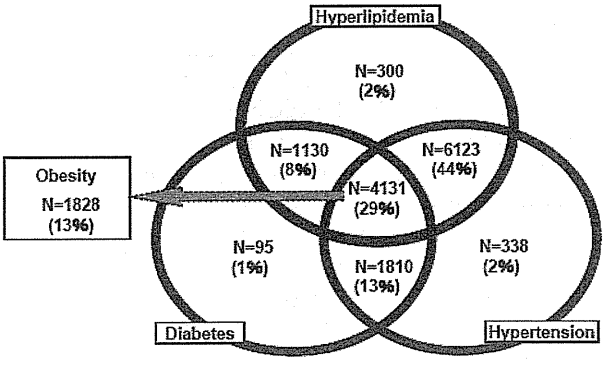

Fig. 1. Concomitant risk factors.

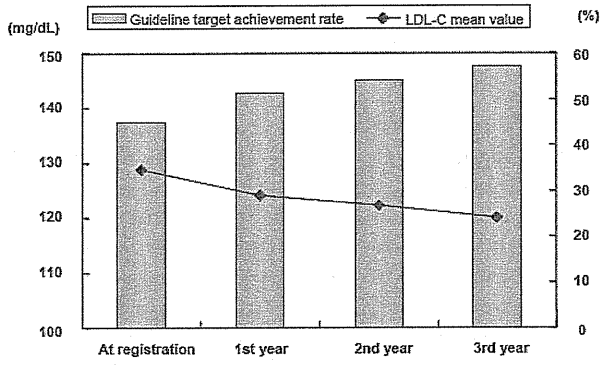

Fig. 2. Changes in 3-year mean values and guideline target achievement rates for LDL-C.

guideline target achievement rates over 3 years. In all patients, LDL-C showed a significant ($p<0.0001$) decrease from 128.8 ± 32.7 to 120.0 ± 29.2 mg/dL. The achievement rate for LDL-C target set in the Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases[9] (<140 mg/dL for patients with two risk factors, <120 mg/dL for patients with three or four risk factors or diabetes, <100 mg/dL for patients with myocardial infarction) showed a significant ($p<0.0001$) increase from 45.0% to 57.1%. Both mean TC and TG showed significant ($p<0.0001$) decreases from 214.9 ± 36.5 to 204.1 ± 33.1 mg/dL and 163.0 ± 119.3 to 147.6 ± 92.1 mg/dL over 3 years, respectively, while HDL-cholesterol (HDL-C) showed a significant increase from 55.2 ± 15.3 to 56.2 ± 15.6 mg/dL ($p<0.0001$). The achievement rate for the therapeutic target values (TC <220 mg/dL for patients with two risk factors, <200 mg/dL for patients with three or four risk factors or diabetes, <180 mg/dL for patients with myocardial infarction, TG <150 mg/dL, HDL-C ≥40 mg/dL) also showed significant ($p<$

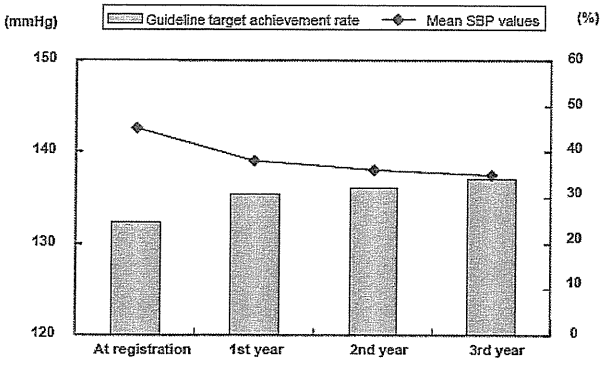

Fig. 3. Changes in 3-year mean values and guideline target achievement rates for SBP.

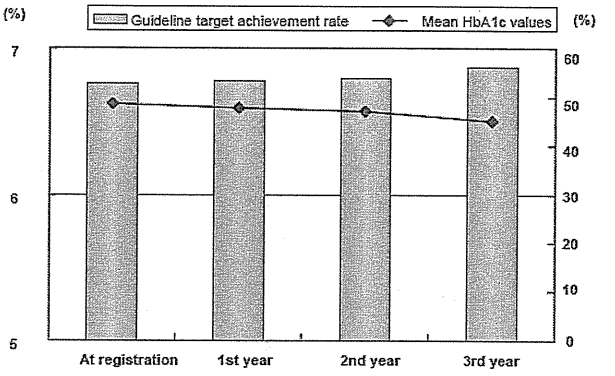

Fig. 4. Changes in 3-year mean values and guideline target achievement rates for HbA1c.

0.0001) improvement from 38.0% to 51.4% for TC, 57.3% to 63.4% for TG, 86.7% to 87.9% for HDL-C, respectively.

3) Blood Pressure

Significant decreases were observed over 3 years for both SBP (from 142.6 ± 15.7 to 137.5 ± 14.3 mmHg) and DBP (from 80.1 ± 10.8 to 77.1 ± 8.7 mmHg; both $p<0.0001$). The achievement rate for the therapeutic target values of the Japanese Society of Hypertension: Guidelines for the management of hypertension (JSH 2004) (<130/85 mmHg for young or midle age adults, <140/90 mmHg for elderly, <130/80 mmHg for patients with diabetes) also showed significant improvement from 24.7% to 34.0% for SBP and from 57.2% to 68.1% for DBP (both $p<0.0001$). Changes of mean SBP values and guideline target achievement rates are shown in **Fig. 3**.

4) Blood Glucose

Mean FBG significantly ($p<0.0001$) fell from 121.2 ± 42.7 to 116.7 ± 37.3 mg/dL and the guideline target achievement rate significantly ($p<0.0001$) increased from 69.6% to 74.6%. Mean HbA1c values also improved from 6.62% to 6.50% ($p<0.0001$). The achievement rate for the therapeutic target values of the Treatment Guide for Diabetes (<6.50%) also showed significant improvement from 52.8% to 56.3%. Changes of mean HbA1c and guideline target achievement rates over 3 years are shown in **Fig. 4**.

5) Use of Therapeutic Drugs

The prescription rates for antihyperlipidemic drugs showed no major changes over 3 years; a drug prescription rate of about 75% was maintained throughout this period. The most common drug class prescribed was HMG-CoA reductase inhibitor (statin) (**Fig. 5a**).

Prescription figures for antihypertensive drugs revealed that about half the patients were prescribed calcium channel blockers (CCBs) throughout the survey period, whereas angiotensin II receptor blockers (ARBs) showed an increase from 22.4% to 35.8% and diuretics increased from 9.2% to 12.5% in 3 years. As a result, the mean number of drugs prescribed/patient increased from 1.45 to 1.62 (**Fig. 5b**). Analysis of the concomitant use of antihypertensive drugs at the time of registration showed concomitant angiotensin-converting enzyme (ACE) inhibitors and CCBs was the most common combination (22% of patients on concomitant medication) and concomitant ARBs and CCBs was the second (20% of patients on concomitant medication). In the third year, ACE inhibitors plus CCBs dropped to 16% and were replaced by ARB plus CCB as the most common combination at 30%.

Among antidiabetic drugs, prescription rates for insulin, biguanides, and anti-insulin resistance drugs increased over 3 years and, as a result, the mean number of drugs prescribed/patient increased from 0.96 to 1.15 (**Fig. 5c**).

6) Cardiovascular Events

The incidence of all cardiovascular events during the 3-year survey period was 15.1/1,000 persons/year. By disease, the incidence rate/1,000 persons/year was 4.4 for fatal and nonfatal myocardial infarction, and 7.8 for fatal and non-fatal stroke.

Over 3 years, the incidence of cardiovascular events was significantly lower in patients who achieved target values of LDL-C, SBP, and HbA1c than in those who did not (**Fig. 6a–c**). In multivariate analysis, the Cox proportional hazard model adjusting for age, gender, and history of myocardial infarction showed a sig-

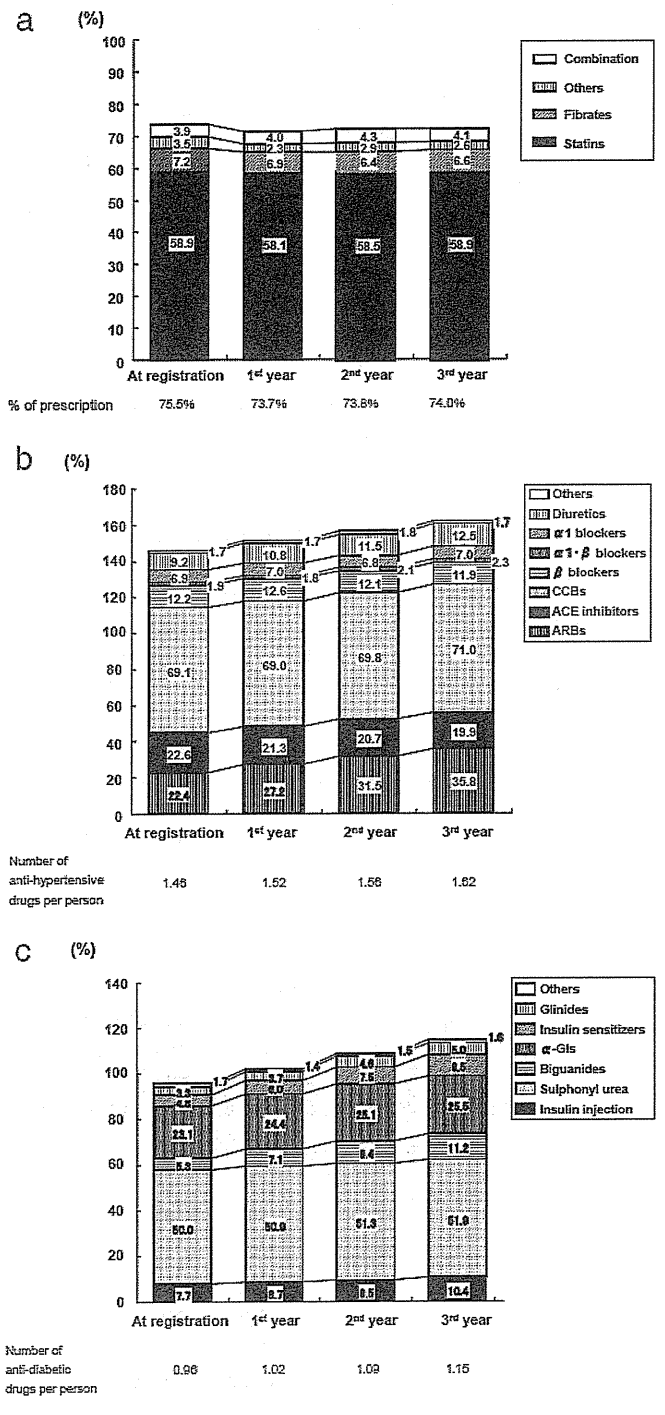

Fig. 5. Prescriptions of drugs and changes over time.

a) Antihyperlipidemic drugs
b) Antihypertensive drugs
CCB, calcium channel blockers; ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor blockers
c) Antidiabetic drugs
α-GIs, alpha-glucosidase inhibitors

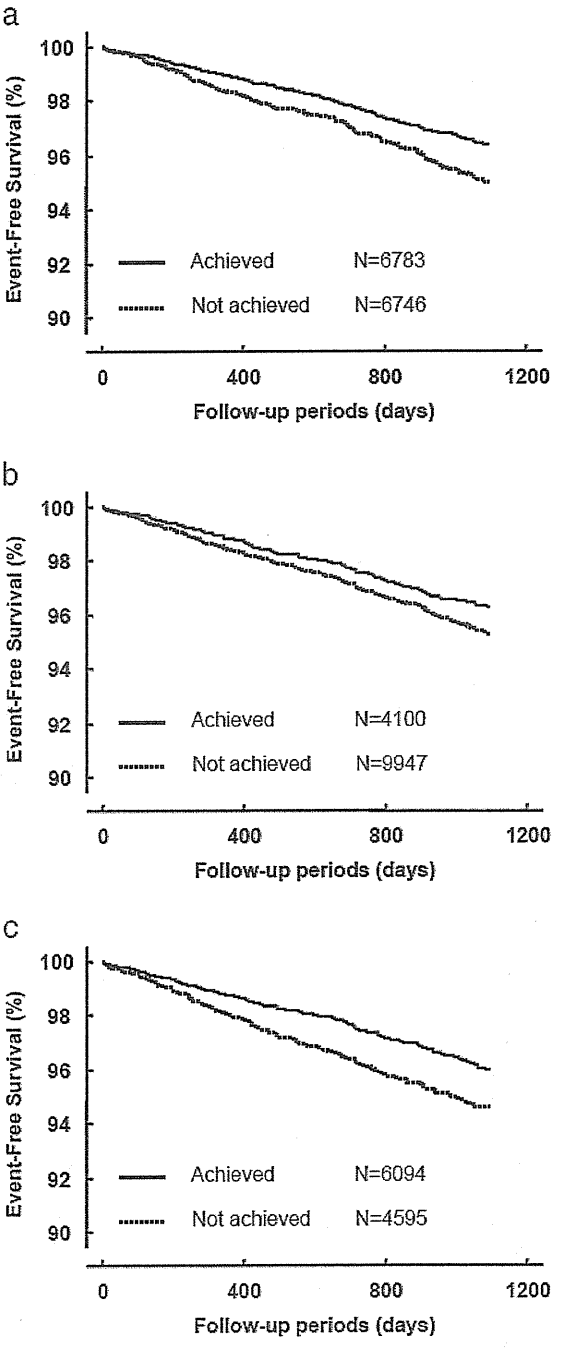

Fig. 6. Effect of guideline target achievement rates on cardiovascular events.

a) LDL-C: Significantly higher event-free survival was observed in achieved group (Log-rank test, $p=0.0001$)
b) SBP: Significantly higher event-free survival was observed in achieved group (Log-rank test, $p=0.0148$)
c) HbA1c: Significantly higher event-free survival was observed in achieved group (Log-rank test, $p=0.0006$)
LDL-C, LDL cholesterol; SBP, systolic blood pressure

Table 2. Results of multivariate analysis

	HR	95%CI	*p*
LDL-C			
Not achieved	1.00	Reference	
Achieved	0.77	0.64–0.93	0.0066
SBP			
Not achieved	1.00	Reference	
Achieved	0.58	0.47–0.71	<0.0001
HbA1c			
Not achieved	1.00	Reference	
Achieved	0.62	0.51–0.75	<0.0001

HRs and CIs were adjusted by age, gender, smoking, alcohol consumption, history of myocardial infarction.
Hr, hazard ratio; CI, confidence interval; LDL-C, LDL cholesterol; SBP, systolic blood pressure

nificantly lower risk for cardiovascular events in patients who achieved target values of LDL-C, SBP, and HbA1c than in those who did not (**Table 2**).

Discussion

In this study, we demonstrated significant associations between the achievement of target values in the guidelines for each disease and cardiovascular events at high risk of CHD under the routine care of general practitioners. Furthermore, we investigated the clinical healthcare activities of general practitioners, mainly by analyzing patterns of drug prescriptions. Based on the results, several effects and problems related to routine healthcare in Japan became apparent.

First, substantial improvements were found in management conditions for hypertension, hyperlipidemia, and diabetes mellitus over the 3-year investigation period. This appears to be due to the healthcare activities of physicians with the introduction of potent drugs such as statins and CCBs, ACE inhibitors and ARBs. On the other hand, no major changes in obesity and smoking were observed that indicated difficulties in changing a patient's lifestyle, such as diet, exercise, and smoking habits.

Target achievement rates among patients taking antihyperlipidemic agents in the Japan Lipid Assessment Program (J-LAP)[12] were 53.1% for TC and 63.4 for LDL-C, whereas we observed slightly lower rates of 51.4% and 57.1%, respectively. This difference was probably because the subjects in the present study had ≥2 CHD risk factors or were secondary prevention cases, which made them more severe cases than those included in J-LAP and therefore more difficult to treat. It is also possible that the participating physicians did not change the treatment target based on the patients' disease state. In the 3 years of the survey, although approximately 60% of patients were prescribed statins, in about 1 in 4 patients, antihyperlipidemic drugs, including statins, were not prescribed. Furthermore, among hypertensive patients, about half did not receive drug treatment and of those who did, about half achieved blood pressure target values; that is, only 1 in 4 patients with hypertension received sufficient antihypertensive treatment, a problem called the "one-half rule"[13].

For hypertension, major changes were seen for drug prescriptions and this appeared to contribute to the increase in the guideline target achievement rate. Among prescriptions, the percentage of ARB showed a marked increase of about 1.6-fold over 3 years; however, prescriptions of ACE inhibitors decreased. This is considered to be caused by several ARBs that have been launched during those years and recent evidence in favor of their inhibitory effects against new-onset diabetes, a renal protective effect[14, 15]. For diuretics, there is concern about metabolic adverse reactions[16] and hence the prescription frequency in Japan had been rather low[17]; however, in HCN we observed a slightly increased prescription rate of these medications over 3 years. The participants in HCN were possibly in the process of reconsidering diuretics based on recommendations for prescription of these agents by the Japan Society of Hypertension and other academic societies made under the influence of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[18] and other studies. This survey showed that patients achieving the SBP guideline target value accounted for only 34.0% even in the third year. It is necessary to introduce more aggressive antihypertensive therapy for better blood pressure management in the future.

Among anti-diabetic drugs, a notable increase in biguanides prescriptions was observed. Since deaths caused by lactic acidosis were reported in the 1970s, biguanides have been largely avoided; however, in recent years several misunderstandings have being resolved and a possible reason in the increased use of these drugs might be the rising incidence in Japan of type 2 diabetes mellitus associated with obesity, which often responds well to these drugs[19].

The most noteworthy result of this survey was that we could confirm that patients who did not achieve guideline target values for hyperlipidemia, hypertension, and diabetes mellitus experienced significantly more events than those achieving the targets. Currently, various diagnosis and treatment guidelines are applied by general practitioners in Japan, but

there are few epidemiological data showing any connection between the achievement of target values and inhibition of cardiovascular events. Therefore, our nationwide HCN data are valuable since they verify the appropriateness of guideline treatment target values and the beneficial effect of their attainment in routine healthcare by general practitioners.

This research was an observational cohort study under routine healthcare; it did not specify what interventions, such as medication or patient guidance, were to be used during the survey period. For this reason, the research allows only limited evaluation of the efficacy of specific treatment methods. However, since the treatments given are analyzed by the research groups in each region every year, the participating physicians have gained increased awareness of the management of lifestyle diseases during the survey period. Therefore this research can be notionally considered a cohort study wherein the test intervention was physicians' awareness. The organization of HCN research groups has deepened discussions and promoted reform of the awareness of physicians, leading to increased guideline achievement rates. This implies that scientific societies and guideline committees should make efforts to undertake activities to promote their guidelines and follow the status of subsequent clinical application. The present data also reconfirm the importance of activities of small-sized, regional hospital-clinic cooperative research groups such as HCN.

Acknowledgment

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Appendix

a) The nationwide-network organization of "HCN research groups"

Administration: Hiroyuki Daida, Department of Cardiology, Juntendo University School of Medicine

Data management and statistical analysis: Takatoshi Kasai, Department of Cardiology, Juntendo University School of Medicine

Participants in the HCN (according to the area): HCN Ebetsu-Sapporo (Junichiro Takahashi, Shinichiro Suzuki, Kazuyoshi Okuno), HCN Sapporo (Naoki Funayama, Yutaka Kadono, Shin Aoki), HCN Hakodate (Hiroshi Oimatsu), HCN Hachinohe (Harumi Mukaida, Toshiyuki Adachi, Naoyuki Ogyu), HCN Morioka (Tomomi Suzuki, Kazumi Ninomiya, Hirozumi Kaneko), HCN Iwaki (Toshikatsu Ichuhara), HCN Shirakawa (Tomiyoshi Saito, Tsuneyoshi Saito, Yoshio Sato, Yasunori Tsukahara, Hidetoshi Utsunomiya), HCN Koga (Kiyoshi Oki, Tadashi Ota, Hirotada Maezawa), HCN Mito (Minoru Murata, Nobuhiro Morooka), HCN Ryomo (Hitoshi Yokozuka, Takao Seki), HCN Gunma (Shuichi Ichukawa, Yoshiaki Takayama, Takashi Kawashima, Masami Kogure), HCN Ota (Nobuyuki Kobayashi, Hiroki Fukushima, Minoru Arisaka), HCN Chuetsu (Masaaki Okabe, Yuya Kitamura, Kyotsu Itakura, Masanosuke Nagao, Shigeru Nakajima), HCN Joetsu (Mitsuaki Yoshioka, Keiichi Takahashi, Satoshi Takano), Chushin HCN (Tetsuji Misawa, Sadahide Okudaira, Kenji Toba, Nagao Mizoue, Ken Miyazawa, Tetsuo Yokoyama), HCN Kazusa (Akira Miyazaki, Jun Tashiro, Hiroya Suzuki), HCN Soka-Yashio (Kan Takayanagi, Hiroko Takagi), HCN Saitama-Seibu (Masayoshi Nagata, Masami Sakurada, Wataru Hirose, Yoshiki Terashi, Tetsuo Yoshikawa), HCN Joto (Shingo Seki, Kenji Noma, Satoshi Inaba, Yoshihiro Tanaka), HCN Chuo (Hiroyuki Daida, Kazunori Shimada, Katsumi Miyauchi, Takatoshi Kasai, Hiroshi Morichika, Hiroyuki Fujii, Hiroshi Hatori, Masafumi Kidokoro), HCN Shibuya (Teruhiko Aoyagi, Takanobu Tomaru, Masahide Shiozaki), HCN Yokohama-Aoba (Yoichi Takeyama, Shigetaka Tokuoka, Masato Nishikawa), HCN Minami-Yokohama (Shinichi Toyama, Koichi Hirao, Hisao Mori, Masaaki Miyakawa), HCN Asahi-Seya (Haruki Musha), HCN Sagami (Kazuo Toyota, Yuji Kakuhari), HCN Shizusei (Shingo Omote, Hideyuki Mukai, Hiroyuki Fukita, Terumoto Fukuchi), HCN Hamamatsu (Chiei Takanaka, Akira Takahashi), HCN Higashi-Mikawa (Michio Suzuki, Akinori Takasawa), HCN Matsusaka (Norimoto Houda, Katsutoshi Makino, Katashi Yamamoto), HCN Kamanza (Naoto Inoue, Hiroshi Fujita, Katsuhiko Komaki, Akira Masumoto), HCN Fushimi (Tameo Nakano, Susumu Handa), HCN Uji-Fushimi (Yoshio Kawano, Ikuzo Nakagawa, Akira Masui), HCN Otsu (Kunihiko Hirose, Atsushi Inoue), HCN Noto (Tadayoshi Takekoshi, Mitsuru Yamagishi, Hideaki Ito), HCN Fukui (Sumio Mizuno, Yoshiharu Yamamoto, Shuichiro Yasuhara), HCN Higashi-Yodogawa (Yasuyuki Kurimoto, Masatoshi Nakao), HCN Osaka (Hidefumi Hamada, Masataka Nagata), HCN Higashi-Osaka (Masayoshi Mishima, Yasutada Morikami), HCN Hokusetsu (Yasunori Horiguchi), HCN Kishiwada (Mitsuo Matsuda, Takashi Uegaito, Tateki Sakamoto, Jinichi Uemura, Itsuo Ikezoe, Itsuro Sugihara, Susumu Nishimura), HCN Wakayama (Hajime Kotoura, Shoji Tanaka), HCN Kobe (Motoshi Takeuchi, Tomohiro Kondo, Chojiro Yamashita, Kotai Haku, Keiji Murakami), HCN

Himeji (Teishi Kajiya, Naoaki Imai, Kazuta Shimizu, Nobuyoshi Daitoh, Toshio Nakano, Shusuke Miwa), HCN Ehime (Jitsuo Higaki, Toshiaki Ashihara, Haruhiko Yamashita, Takaaki Ochi, Wataru Matsubara), HCN Mitoyo-Kanonji (Mamoru Hirohata, Masaaki Ueeda), HCN Tokushima (Yoshikazu Hiasa), HCN Kochi (Yoshinori Doi, Masanori Nishinaga, Masaru Kimura, Hiroyuki Ikefuji, Isui Ueta), HCN Okayama (Minoru Ueda), HCN Kurashiki (Kazuaki Mitsudo), HCN Tottri (Yasuyuki Yoshida, Kohei Tamura, Masato Yoshida), HCN Izumo (Tsuyoshi Oda, Tomoyuki Furuse, Akio Imaoka, Takashi Nishio, Tadashi Hata), HCN Matsue (Nobuo Shiode, Noriji Yuhara, Nobuaki Nakamura), HCN Hagi (Yasuo Matsuda, Michihiro Kono), HCN Tokuyama (Hiroshi Ogawa, Setsuya Maeda), HCN Fukuoka (Takuya Tsuchihashi, Michio Ueno, Kikuo Sakai), HCN Chikuho (Shuichi Okamatsu, Masaharu Kaneda, Koji Okabe, Naoya Ito), HCN Omuta (Kenzo Sugi, Tatsuro Hiraki, Koji Matsuyama, Takashi Ishizaki, Nobue Sakanishi, Nobuaki Ochi, Toru Minami, Hiroshi Matsunaga, Hisakazu Yoshimura), HCN Nagasaki (Toshio Nunobiki, Yasuhiko Oku), HCN Kumamoto (Takashi Honda, Yutaka Horio, Kazuo Goto, Shojiro Naomi), HCN Kagoshima (Kazuhiko Nakamura, Shinichiro Egawa), HCN Nobeoka (Takeshi Yamamoto).

References

1) Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare: Vital Statistics of Japan 2005
2) Kannel WB: Risk factors in hypertension. J Cardiovasc Pharmacol, 1989; 13 (Suppl 1): S4-10
3) Futterman LG, Lemberg L: The Framingham Heart Study: a pivotal legacy of the last millennium. Am J Crit Care, 2000; 9: 147-151
4) Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M: Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke, 2003; 34: 2349-2354
5) NIPPON DATA80 Research Group: Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J, 2006; 70: 1249-1255
6) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, and Yokode M. Risk factors of atherosclerotic disease. Excutive summary of Japan Atheroscleosis Society (JAS) guideline for diagnosis and prevention of atherosclerosis cardiovascular disease for Japanese. J Atheroscler Thromb, 2007; 14: 267-277
7) Nakamura T, Tsubono Y, Kameda-Takemura K, Funahashi T, Yamashita S, Hisamichi S, Kita T, Yamamura T, Matsuzawa Y; Group for the Research for the Association between Host Origin and Atherosclerotic Diseases under the Preventive Measure for Work-related Diseases of the Japanese Labor Ministry: Magnitude of sustained multiple risk factors for ischemic heart disease in Japanese employees: a case-control study. Jpn Circ J, 2001; 65: 11-17
8) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, and Yokode M: Metabolic syndrome. J Atheroscler Thromb, 2008; 15: 1-5
9) The Japanese Society of Hypertension: Japanese Society of Hypertension Guidelines for the Management of Hypertension 2004. Hypertens Res, 2006; 29 Suppl: S1-105
10) Japan Atherosclerosis Society: Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases 2002. J Atheroscler Thromb, 2002; 9: 1-27
11) Treatment Guide for Diabetes 2004-2005. Japan Diabetes Society 2004
12) Teramoto T, Kashiwagi A, Mabuchi H, J-LAP Investigators: Status of lipid-lowering therapy prescribed based on recommendations in the 2002 report of the Japan Atherosclerosis Society Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese Adults: a study of the Japan Lipid Assessment Program (J-LAP). Curr Ther Res, 2005; 66: 80-95
13) Hyman DJ, Pavlik VN: Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med, 2001; 345: 479-486
14) Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; for the LIFE study group: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE): a randomized trial against atenolol. Lancet, 2002; 359: 995-1003
15) Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; for the RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med, 2001; 345: 861-869
16) Nader PC, Thompson JR, Alpern RJ: Complications of diuretic use. Semin Nephrol, 1988; 8: 365-387
17) Ohta Y, Tsuchihashi T, Fujii K, Matsumura K, Ohya Y, Uezono K, Abe I, Iida M: Improvement of blood pressure control in a hypertension clinic: a 10-year follow-up study. J Hum Hypertens, 2004; 18: 273-278
18) The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA, 2002; 288: 2981-2997
19) UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34): Lancet, 1998; 352: 854-865

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特集 転倒危険者の早期発見から予防まで —最新のエビデンスから— 各論

KEY WORD ●慢性期病院 ●転倒・転落 ●アセスメントシート

1．病因，病態と転倒
5）慢性期病院における転倒・転落防止対策：アセスメントシートの評価

宮野伊知郎
西永　正典

SUMMARY

慢性期病院の入院患者は慢性疾患を有した高齢患者が多くを占め，転倒・転落のハイリスクと考えられる．病院での転倒・転落予防対策として，アセスメントシートを用いた入院患者の転倒・転落リスク評価が行われている．慢性期病院での検討において，年齢70歳以上，転倒歴あり，活動領域の障害あり，認識力の障害ありが入院中の転倒・転落と関連を認めた．今後，評価者間の評価のばらつきを少なくする工夫や，転倒・転落予防対策の立案・実践に役立つ項目を追加するなどの見直しが，各病院において繰り返し行われることが必要である．

はじめに

慢性期病院の入院患者は，急性期を脱して病状は安定したが長期間の治療を必要とする，慢性疾患を有した高齢患者が多くを占める．入院患者の転倒・転落(以下，転倒)は，患者の病態や心身の状態に大きく影響を受けることが知られており，慢性期病院の入院患者は転倒のハイリスクと考えられる．心身の機能低下を来した高齢患者が転倒に至ると，骨折などの障害や，その治療のための入院期間の長期化によって，さらなる機能低下を生じ，日常生活動作能力(ADL)の低下，ひいては生活の質(QOL)の低下を来すこととなる．慢性期病院における転倒予防対策は，大変重要な課題とみなされている．

転倒・転落リスクのアセスメント

入院患者における転倒防止対策として，一般的に患者個々の転倒リスクの把握を行った後，予防的対策を立案し介入を行う手法がとられている．したがって，転倒リスクの把握は，ハイリスク者を効果的に発見し，予防的介入につなげることを目的としている．入院患者の転倒の要因は多岐にわたるが，その多くの要因の中で入院患者の転倒と関連の強い因子を抽出する必要があり，多くの試みがなされている．海外の報告では，強い転倒リスクとして精神症状・認知機能障害，過去の転倒歴，脳卒中の後遺症，排泄動作の障害，多剤服用，視・聴覚障害，バランス障害などが挙げられている[1]．また，多くの要因からより有用な項目を選定し，簡易なアセスメントツールが作成されており，Oliverらは転倒の既往，看護師の判断による患者の精神状態，移動能力，トイレの使用頻度，視力障害の5項目のみが有用な調査項目であったと報告している[2]．

現在，病院や施設における転倒リスクの把握のために，アセスメントシートが活用されている．代表的なアセスメントシートである日本看護協会による転倒・転落アセスメントシートでは，「A：年齢」「B：性別」「C：既往歴」「D：感覚」「E：機能障害」「F：活動領域」「G：認識力」「H：薬剤」「I：排泄」を評価する(表1)．評価した各項目は，それぞれ点数化し合計点数(評価スコア)によって危険度Ⅰ・Ⅱ・Ⅲに分類される．このアセスメントの内容および点数は，各施設の分析データに基づき定期的に見直すこ

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表1　転倒転落アセスメント・スコアシート(例)

分類	特徴	評価スコア	評価スコア / / /
A 年齢	70歳以上，9歳以下	2	
B 性別	男性	1	
C 既住歴	転倒転落したことがある 失神したことがある	2	
D 感覚	視力障害がある，聴力障害がある	1	
E 機能障害	麻痺がある，しびれ感がある 骨，関節に異常がある(拘縮，変形)	3	
F 活動領域	足腰の弱り，筋力の低下がある 車椅子・杖・歩行器を使用している 移動に介助が必要である ふらつきがある 寝たきりの状態である	3	
G 認識力	見当識障害，意識混濁，混乱がある 痴呆がある 判断力，理解力の低下がある 不穏行動がある 記憶力の低下があり，再学習が困難である	4	
H 薬剤	□鎮痛剤　□麻薬剤　□睡眠安定剤 □抗パーキンソン剤　□降圧利尿剤 □浣腸緩下剤　□化学療法	それぞれ 1	
I 排泄	□尿，便失禁がある　□頻尿がある □トイレ介助が必要　□尿道カテーテル留置 □夜間トイレに行く　□トイレまで距離がある	それぞれ 2	
		合計	
		危険度	

日本看護協会編：組織でとりくむ医療事故防止．看護管理者のためのリスクマネジメントガイドライン，p31，2000年より引用

とが推奨されている．

われわれが慢性期病院(高知県N病院)において，アセスメントシートの項目と入院中の転倒との関連を検討した結果を紹介させていただく．対象者は入院患者393人，平均年齢は81歳であり，70歳以上が352人，全体の89.6%を占める．男性151人(38.4%)，女性242人(61.6%)であった．対象者全体における各項目の該当者数(頻度)は，既往歴ありが185人(47.1%)，感覚障害ありが187人(47.6%)，機能障害ありが225人(57.3%)，活動領域の障害ありが307人(78.1%)，認識力障害ありが185人(47.1%)，薬剤の項目のうち1剤でも内服ありが233人(59.3%)，排泄の項目のうち1つでも該当ありが346人(88.0%)であった．これらから，心身の機能障害を有する入院患者が多いことが示され，慢性期病院の特徴と考えられる．入院中の転倒は38人(9.7%)に認めた．転倒の発生との関連についての検討では，年齢70歳以上，既往歴あり，活動領域の障害あり，認識力障害ありの4項目において，それぞれ転倒発生の頻度の増加を認めた(表2)．特に既往歴の転倒発生に対する関連は強く，年齢，性別で調整したオッズ比は3.7(95%C.I.=1.7～8.0)であ

表2　アセスメントシート各項目と転倒・転落発生との関連，人数(%)

	転倒・転落なし n=355	転倒・転落あり n=38	p
A 年齢70歳以上，(%)	314(88.5)	38(100)	0.022
B 性別 男性，(%)	135(38.0)	16(42.1)	0.726
C 既往歴あり，(%)	157(44.2)	28(73.7)	0.001
D 感覚障害あり，(%)	163(45.9)	24(63.2)	0.059
E 機能障害あり，(%)	199(56.1)	26(68.4)	0.169
F 活動領域障害あり，(%)	272(76.6)	35(92.1)	0.037
G 認識力障害あり，(%)	160(45.1)	25(65.8)	0.017
H 薬剤，(%)	213(60.0)	20(52.6)	0.390
I 排泄，(%)	311(87.6)	35(92.1)	0.599

薬剤，排泄は項目内の1つでも該当した人数を記載

った．既往歴ありは，感覚，機能障害，活動領域，認識力それぞれの障害ありと有意な関連を認めており，このことから転倒の既往を有する高齢者は既に心身の機能低下を来しており，強い転倒のハイリスク状態であると考え得る．また，転倒経験は骨折などの外傷を受けなかったとしても，再び転倒するのではないかという不安や恐怖感を生じさせ，それがさらに転倒を助長させることが指摘されている．活動領域については，既に多くの文献で述べられているように「足腰の弱り，筋力の低下がある」「車椅子・杖・歩行器を使用している」「移動に介助が必要である」「ふらつきがある」が転倒発生と有意な関連を認め，転倒・転落アセスメントにおいては重要な項目と考えられる．認識力の障害も同様に転倒のアセスメントには重要な項目である．

転倒・転落アセスメントシートの課題

アセスメントシートによる転倒リスクの評価を行う際，いくらかの問題点がある．1つは，各項目内容の定義が定められていない点が挙げられる．例えば，視力障害，聴力障害の定義がなく，評価者の判断によって結果にばらつきがみられる．同様なことが活動領域，認識力などほかの項目でもみられる．今後はそれぞれの病院・施設において各項目の定義を定め，評価者間のばらつきの少ないアセスメントシートの作成が必要である．2つめには，転倒の予防的ケアプランの立案，さらにその実践に役立つアセスメントシートの作成が必要という点である．病院における転倒発生の要因は，病院の機能や入院患者の特徴によって大きく異なるため，もともとアセスメントシートは各病院それぞれの状況にあったシートの作成・見直しが前提条件となっている．その際，転倒事例について転倒時の場所や時間などの状況を詳細に検証し，考えられる要因をアセスメントシートに反映させることが望ましい．

おわりに

病院・施設などの現場では，アセスメントシートを用いた転倒リスク評価を活用した転倒予防対策の取組みが行われている．しかし，その一方で患者の病状や症状は日々変化しており，アセスメントシートだけでは十分対応できない場合も多くみられる．様々な状況に対応するために，医師・看護師だけでなく，薬剤師・理学療法士・栄養士などの多職種間の連携による総合的アプローチが必要と考えられる．

文　献

1) Perell KL et al：Fall risk assessment measures：an analytic review. J Gerontol A Biol Sci Med

Sci 56：M761-M766, 2001.
2) Oliver D et al：Development and evaluation of evidence based risk assessment tool (STRATIFY) to predict which elderly inpatients will fall：case-control and cohort studies. BMJ 315：1049-1053, 1997.

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Clinical Profiles of Hypertrophic Cardiomyopathy With Apical Phenotype

— Comparison of Pure-Apical Form and Distal-Dominant Form —

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Background: Hypertrophic cardiomyopathy (HCM) with an apical phenotype, in which hypertrophy of the myocardium predominantly involves the apex of the left ventricle, is not uncommon in Japan, but its morphologic variations are not well recognized. The aim of this study was to investigate if these variations have different clinical characteristics although they are still confused to be the same.

Methods and Results: Patients with the apical phenotype were divided into 2 groups, the "pure-apical" form and the "distal-dominant" form, and their clinical profiles were compared. From the study cohort of 264 patients with HCM, 80 (30%) were classified as having the apical phenotype: 51 with the pure-apical form and 29 with the distal-dominant form. The age at diagnosis was approximately 60 years, and in both groups the majority were male. The distal-dominant group had a significantly larger left atrial diameter (43 vs 39 mm) and higher ratio of proven familial HCM (28 vs 6%), and were more symptomatic (New York Heart Association ≥3) at presentation (17 vs 0%). The event-free rate of cardiovascular events in patients with the distal-dominant form was significantly worse (log-rank P=0.012) than that in patients with the pure-apical form (follow-up period: ≈5 years).

Conclusions: The 2 phenotypes of apical HCM should be recognized and distinguished clinically. (*Circ J* 2009; **73:** 2330–2336)

Key Words: Apex; Hypertrophic cardiomyopathy; Phenotypes

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with heterogeneous morphological, functional, and clinical features, although left ventricular hypertrophy (LVH), particularly asymmetric septal hypertrophy (ASH), is the most characteristic feature.[1–5] The apical phenotype of HCM, in which hypertrophy of the myocardium predominantly involves the apex of the left ventricle (LV), was originally reported in Japan as a subset of non-obstructive HCM characterized by a striking ECG pattern of giant negative T (GNT) waves associated with an angiographic "spade-shaped deformation of the LV cavity" at end-diastole.[6–12] Detailed observation of the morphology by echocardiography has shown that the apical phenotype can be divided into a "pure-apical" form and a "distal-dominant" form (**Figures 1a,b**).[13] Although those phenotypes are sometimes confused, they may have different clinical characteristics, so we investigated the clinical characteristics of HCM patients with the apical phenotype in the context of comparing the 2 forms.

Methods

Subjects

We retrospectively studied 264 consecutive patients with HCM (180 men, 84 women; mean age, 56±15 years; age range, 9–87 years). All patients were evaluated at the Kochi Medical School Hospital between 1982 and 2006 for confirmation of diagnosis, risk assessment and symptom management. The diagnosis of HCM was based on 2-dimensional (D) echocardiographic demonstration of unexplained (LVH), ie, maximum LV wall thickness ≥15 mm. Exclusion criteria included systemic or cardiovascular diseases capable of generating LVH, such as uncontrolled hypertension and aortic valve stenosis. The study was approved by the Ethics Committee on Medical Research of Kochi Medical School.

Clinical Evaluation

Evaluation of patients included medical history, clinical examination, 12-lead ECG, M-mode, 2-D and Doppler echocardiography, and ambulatory 24-h Holter ECG analysis.

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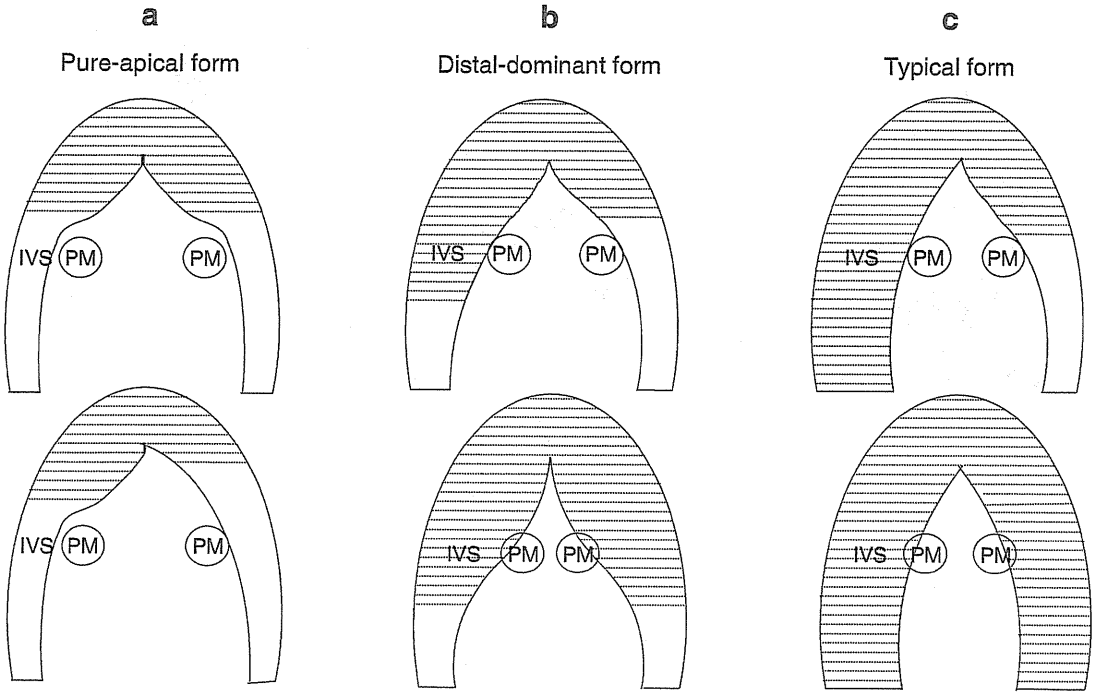

Figure 1. Definitions of the 2 morphologic patterns in HCM with an apical phenotype. (**a**) "Pure-apical" form: hypertrophy (≥15 mm) is confined to the LV apex below the PM level. (**b**) "Distal-dominant" form: apical hypertrophy extends to the IVS without basal septal hypertrophy. (**c**) "Typical" form of HCM: segmental or diffuse hypertrophy involving the basal portion of the LV. HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LV, left ventricle; PM, papillary muscle.

The severity and distribution of the LVH were assessed in the parasternal short-axis plane at the level of the mitral valve and the papillary muscles.[14,15] LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were measured from M-mode and 2-D images obtained from parasternal long-axis views, and fractional shortening [(LVEDD−LVESD)/LVEDD×100] was calculated. Mitral inflow velocities were determined using pulsed-wave Doppler with the sample volume positioned at the tips of the mitral leaflets in the 4-chamber view. Peak E-wave velocity (E), peak A-wave velocity (A) and E/A ratio were recorded. Tissue Doppler imaging was performed in the pulse-Doppler mode to allow for a spectral display and recording of mitral annulus velocities at the septal and lateral corners. The peak early diastolic (Ea) velocity was measured, and the E/Ea ratio as an index of LV diastolic dysfunction was calculated.[16,17] The LV outflow tract (LVOT) gradient was calculated from the continuous-wave Doppler using the simplified Bernoulli equation.

Using the LV wall thickness assessed by echocardiography, we classified the patients into 3 morphologic patterns: (1) hypertrophy (≥15 mm) confined to the LV apex below the papillary muscle level (pure-apical form) (**Figure 1a**), (2) apical hypertrophy extending to the interventricular septum (IVS) without basal septal hypertrophy (distal-dominant form) (**Figure 1b**), and (3) typical HCM presenting as segmental or diffuse hypertrophy involving the basal portion of the LV, even in patients demonstrating the greatest wall thickness in the apical segment (**Figure 1c**).

Peripheral blood samples were collected for the measurement of plasma B-type natriuretic peptide (BNP) at the time of clinical evaluation.

Data on survival and the clinical status of patients were obtained during serial clinic visits or by direct communication with patients and their cardiologists for patients who were followed up at other institutions.

For survival analysis, 3 types of cardiovascular death were defined: (1) sudden and unexpected death (including resuscitated cardiac arrest), in which collapse occurred in the absence of, or <1 h from, the onset of symptoms in patients who previously experienced a relatively stable or uneventful clinical course; (2) heart failure-related death, which was in the context of progressive cardiac decompensation ≥1 year before death; and (3) stroke-related death, which occurred as a result of probable or proven embolic stroke. Major morbid events included (1) hospitalization for heart failure, (2) stroke, and (3) sustained ventricular tachycardia (VT), defined as >30 consecutive ventricular beats or associated with hemodynamic instability.

Statistical Analysis

Statistical analysis was performed using SPSS (version 14.0) statistical software (SPSS Inc, Chicago, IL, USA). All data are expressed as mean±SD (range) or frequency (percentage). Differences in continuous variables were assessed using Student's t-test. Pearson's chi-square test was used for comparisons between non-continuous variables, and Fisher's exact test was used when the expected frequency was lower than 5. Survival estimates were calculated by the Kaplan-Meier method and log-rank test. Statistical significance was defined as $P \leq 0.05$. The BNP level was subjected to logarithmic transformation for statistical analysis.

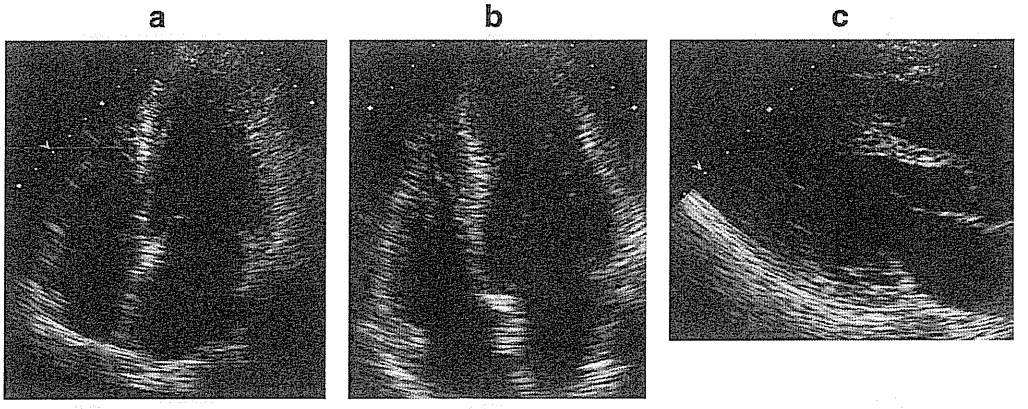

Figure 2. Echocardiographic features in patients with an apical phenotype. (**a**) Apical 4-chamber view in a patient with the pure-apical form. Left ventricle wall thickening is confined to the most distal region of the apex, below the papillary muscle level. (**b**) Apical 4-chamber view in a patient with the distal-dominant form. Hypertrophy extends to the interventricular septum without basal septal hypertrophy. (**c**) Parasternal long-axis view in a patient with the distal-dominant form. Hypertrophy is detectable in the parasternal cross-sectional planes.

Table 1. Echocardiographic and Electrocardiographic Characteristics of Patients With Hypertrophic Cardiomyopathy at Initial Evaluation

	"Pure-apical" form (n=51)	"Distal-dominant" form (n=29)	P value
IVS, mm	11.0±1.48 (8–14)	12.2±1.50 (8–14)	0.001
PW, mm	10.8±1.42 (8–13)	11.4±1.74 (8–14)	0.101
Maximum wall thickness at PM level, mm	12.3±1.32 (10–14)	17.2±2.79 (15–29)	<0.001
Left atrial diameter, mm	39±5.1 (28–50)	43±5.7 (30–56)	0.003
LV end-diastolic diameter, mm	47±4.5 (38–60)	49±5.6 (28–55)	0.132
LV end-systolic diameter, mm	27±4.7 (19–42)	28±5.2 (18–36)	0.531
Fractional shortening, %	42±6.6 (25–59)	43±7.4 (32–58)	0.487
E/A ratio	1.1±0.50 (0.5–2.7) (n=37)	1.1±0.43 (0.6–2.1) (n=20)	0.685
E/Ea (septal)	8.8±2.27 (5.5–14.0) (n=19)	11.9±3.80 (6.7–21.1) (n=15)	0.005
E/Ea (lateral)	6.0±1.41 (4.1–9.0) (n=19)	8.6±2.85 (3.8–14.1) (n=15)	0.005
LVOTO, n (%)	0 (0%)	0 (0%)	
Apical aneurysm, n (%)	2 (4%)	2 (7%)	0.620
Paradoxical jet, n (%)	4 (8%)	6 (21%)	0.155
Midventricular obstruction or apical obliteration, n (%)	0 (0%)	4 (14%)	0.015
Rhythm (AF), n (%)	5 (10%)	4 (14%)	0.716
Abnormal Q wave, n (%)	1 (2%)	2 (7%)	0.296
ST-T change, n (%)	49 (96%)	28 (97%)	1.000
GNT, n (%)	25 (49%)	16 (55%)	0.597
NSVT, n (%)	5 (10%)	3 (10%)	1.000
Pacemaker implantation, n (%)	1 (2%) (for slow AF)	1 (3%) (for SSS: AF, brady-tachycardia)	1.000

Data are mean±SD (range) or number (%).
IVS, interventricular septum [thickness]; PM, papillary muscle; PW, posterior wall [thickness]; LV, left ventricular; E, peak E-wave velocity; A, peak A-wave velocity; Ea, peak early diastolic mitral annulus velocity on tissue Doppler imaging; LVOTO, LV outflow tract obstruction >30 mmHg; AF, atrial fibrillation; GNT, giant negative T waves; NSVT, nonsustained ventricular tachycardia.

Results

Baseline Echocardiography and Electrocardiography

From the study cohort of 264 patients, 80 (30%) were classified as having the apical phenotype (by definition, no patient demonstrating basal interventricular septal hypertrophy (≥15 mm)): 51 patients (19%) with the pure-apical form (**Figure 2a**) and 29 patients (11%) with the distal-dominant form (**Figures 2b,c**). The echocardiographic and electrocardiographic characteristics of these 2 groups at initial evaluation are summarized in **Table 1**. LV systolic function was preserved in all patients with the apical phenotype. In patients with the distal-dominant form, the left atrial diameter was larger and the E/Ea ratio was higher than in the patients with pure-apical form, although the LVEDD, LVESD, %FS, and E/A ratio were not different between the groups. None of the patients showed LVOT obstruction (pressure gradient at rest ≥30 mmHg). On the other hand, midventricular obstruction or apical obliteration was frequently seen in patients with the distal-dominant form. Half of the patients with both the pure-apical and distal-dominant forms showed GNT waves on ECG (defined as a depth ≥10 mm). There were no differences between the 2 groups in the frequency of nonsustained VT and pacemaker implantation.

Baseline Clinical Characteristics

The clinical characteristics of patients with the pure-apical and distal-dominant forms at presentation are summarized in **Table 2**. The age at diagnosis in the patients with each

Table 2. Clinical Characteristics of Patients With "Pure-Apical" or "Distal-Dominant" Form of Hypertrophic Cardiomyopathy at Initial Evaluation

	"Pure-apical" form (n=51)	"Distal-dominant" form (n=29)	P value
Age, years	61±13 (24–87)	62±11 (30–80)	0.668
Male, n (%)	42 (82%)	24 (83%)	0.963
Age at diagnosis, years	59±13 (24–87)	60±11 (30–80)	0.746
Proven familial HCM, n (%)	3 (6%)	8 (28%)	0.014
Family history of sudden death, n (%)	6 (12%)	7 (24%)	0.208
Reason for diagnosis, n (%)			
Symptoms	19 (37%)	15 (52%)	0.208
Incidental findings	32 (63%)	14 (48%)	
Symptoms at presentation, n (%)	27 (53%)	20 (69%)	0.162
Palpitation	3 (6%)	6 (21%)	0.065
Syncope	2 (4%)	1 (3%)	1.000
Chest pain	23 (45%)	11 (38%)	0.533
NYHA class at presentation, n (%)			
I	36 (71%)	14 (48%)	0.048
II	15 (29%)	10 (35%)	0.638
III and IV	0 (0%)	5 (17%)	0.005
BNP, pg/ml	104±120 (4–476) (n=27)	300±424 (16–1,920) (n=20)	0.013
Hypertension, n (%)	26 (51%)	12 (41%)	0.408
Antihypertensive medications, n (%)	18 (35%)	10 (34%)	1.000

Data are mean±SD (range) or number (%).
NYHA class, New York Heart Association class; BNP, plasma B-type natriuretic peptide.

form was 59 and 60 years, respectively. The majority (>80%) of the patients in both groups were male. The distal-dominant group had a significantly higher ratio of proven familial HCM with at least 1 relative who had an unequivocal diagnosis. All 3 patients with the pure-apical form and proven familial HCM were diagnosed at a relatively young age (ages at diagnosis: 29, 43 and 45 years, respectively). Although the reason for diagnosis was not different in the 2 groups, more patients with the distal-dominant form experienced significant dyspnea (New York Heart Association (NYHA) ≥3). Of the 5 patients with NYHA ≥3, all had a history of hospitalization for treatment of heart failure and 4 had paroxysmal or chronic atrial fibrillation (AF). One patient had severe mitral valve regurgitation because of mitral annular dilatation (left atrial diameter 80 mm) and coaptation loss of the mitral valve. He later underwent mitral annuloplasty (no findings of chordal rupture). The other 4 patients had heart failure symptoms because of diastolic dysfunction. At initial evaluation, the BNP level was significantly higher in patients with the distal-dominant form. None of the patients in either group underwent cardioverter-defibrillator implantation.

Clinical Course

The mean follow-up period in the pure-apical and distal-dominant groups was 5.4±5.1 and 4.3±4.9 years, respectively. No patient progressed to the dilated phase of HCM. There were no cardiovascular deaths among the 51 patients with the pure-apical form during the follow-up period (there were 4 non-cardiovascular deaths). On the other hand, 2 patients with the distal-dominant form died a cardiovascular death (sudden death in 1 patient and heart failure in the other). The patient who died suddenly had had AF since he was diagnosed as having apical hypertrophy and died suddenly at the age of 77 years while working as a fisherman. The patient who died of heart failure had a family history of sudden death (2 daughters) and her severe heart failure was considered to be caused by diastolic dysfunction. Cardiac amyloidosis was not detected and she died at the age of 73 years. There were additional cardiovascular events

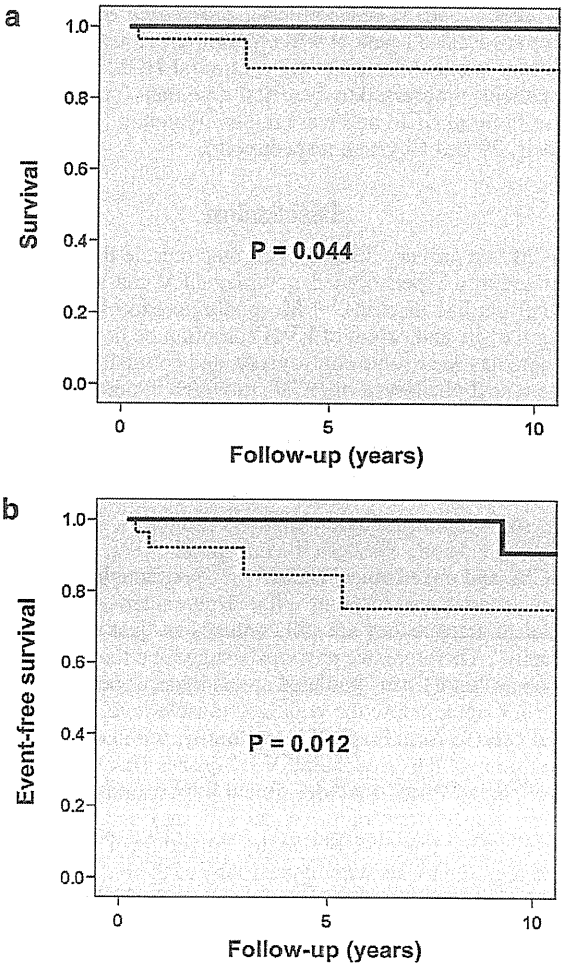

Figure 3. Kaplan-Meier event-free survival. (**a**) Occurrence of cardiovascular death during follow-up. Log rank for trend P=0.044. (**b**) Occurrence of cardiovascular events during follow-up. Log rank for trend P=0.012. ——, Pure-apical form; ·····, Distal-dominant form.

(major morbid events) in each group (stroke in 1 patient with the pure-apical form and hospitalization for heart failure in 2 patients with the distal-dominant form). The admissions of the latter 2 patients were basically because of diastolic dysfunction. **Figure 3b** shows that the event-free rate of cardiovascular events (cardiovascular deaths and major morbid events) in patients with the distal-dominant form was significantly worse (log-rank P=0.012) than that in patients with the pure-apical form.

Paroxysmal or chronic AF was detected in 10 (20%) of the 51 patients with the pure-apical form: 5 presented with AF at the initial evaluation and the other 5 patients experienced AF during the follow-up period (incidence, 1.9%/year). Of the patients with the distal-dominant form, 8 had AF (28%): 4 already had AF at the initial evaluation and the other 4 patients experienced AF after the initial evaluation (incidence, 3.3%/year). Of the 5 patients who suffered from cardiovascular events, 4 already had AF.

Longitudinal Morphologic Changes

The hypertrophy had extended to the IVS in some patients. Hypertrophy progressed in 2 of the 29 patients with the distal-dominant form to the typical form. Hypertrophy also progressed in 7 of the 51 patients with the pure-apical form; 2 of them, who were relatively young (ages at diagnosis: 24 and 41 years, respectively), progressed to the typical form of HCM (1 patient was reported previously), although neither was confirmed to have familial HCM.[18] The other 5 patients progressed to the distal-dominant form; 2 of them had familial HCM and were relatively young (ages at diagnosis: 29 and 45 years, respectively).

Discussion

HCM is a primary disease of cardiac muscle that is characterized by a hypertrophied, nondilated LV unassociated with other cardiac diseases.[1–5] Morphologic expression regarding the site and extent of LVH can often be heterogeneous. There has been some controversy, and confusion, regarding the apical phenotype of HCM, in which hypertrophy of the myocardium predominantly involves the apex of the LV, because of the different diagnostic modalities used by investigators and the various morphologic presentations of apical hypertrophy.[6–12,18–24] Even in the apical phenotype, there are several morphologic variations and terms, including the Japanese form, Western form, apical ASH, pure apical HCM, and mixed apical HCM.[6,8,10–13] Although those variations may have different clinical characteristics, in daily clinical practice they are still confused as "just apical hypertrophy". Therefore, we previously suggested the use of terms such as "pure form" (isolated apical hypertrophy, limited to the LV apex below the papillary muscle level: **Figure 1a**) and "mixed form" (apical hypertrophy, with coexistent hypertrophy of the distal/basal IVS: **Figures 1b,c**).[13] Although the "mixed form" includes apical hypertrophy with coexistent hypertrophy of the distal IVS and occasionally the basal septum, now we divide the "mixed form" into 2 types and regard patients with hypertrophy of the basal IVS, even in cases demonstrating the greatest wall thickness in the apical segment, as part of the common disease spectrum of HCM ("typical" HCM: **Figure 1c**). Recently, Choi et al reported the phenotypic spectrum and clinical characteristics of apical HCM and they used the term "mixed type", defined as presenting with hypertrophy of the IVS in which the hypertrophy was greatest in the apical segments, but did not extend to the basal segments[25] (**Figure 1b**). Because they used the term "mixed type" (or "mixed form") differently to our previous definition, here we use a new term "distal-dominant form" to indicate apical hypertrophy extending to the IVS without basal septal hypertrophy (**Figure 1b**). In the present study, we focused on the apical phenotype (**Figures 1a,b**) and to the best of our knowledge this is the first report of the longitudinal clinical profiles of HCM patients with the apical phenotype from the viewpoint of comparing the pure-apical and distal-dominant forms.

Clinical Background

In the present study, the mean age of patients at diagnosis was approximately 60 years and the majority in both subtypes were male. Our data are in accordance with previously reported Japanese data for apical HCM.[6–9] The prevalence of GNT waves on ECG, which has been reported as a characteristic hallmark of apical hypertrophy (the so-called "Japanese type"), was the same in patients with either the pure-apical or distal-dominant form. The presence of mild hypertension was also similarly seen in both subtypes. Therefore, it is difficult to distinguish these 2 groups by clinical background factors such as age, sex, and ECG features. A significant difference between the 2 groups was only seen in the prevalence of proven familial HCM. A family history of HCM was rare in patients with the pure-apical form (3 (6%) of 51 patients), whereas 28% of the patients with the distal-dominant form were confirmed as having familial HCM. We presume that many cases of the pure-apical form may not be caused by a single mutation that is transmitted with a Mendelian autosomal dominant pattern of inheritance. The age at diagnosis of HCM in these 3 patients with the pure-apical form and familial HCM was relatively young in the present cohort (<45 years old). The relatives of these 3 patients with the pure-apical form and an unequivocal diagnosis of HCM did not show apical hypertrophy, but rather the typical form of HCM (hypertrophy involving the basal portion of the LV).

Clinical Manifestations

Patients with the distal-dominant form were significantly more limited (NYHA ≥3) at presentation and were also more prone to have left atrial enlargement on echocardiography, presumably as a consequence of elevated filling pressure because of impaired LV relaxation. Although the number of the patients was limited in our study, the E/Ea ratio as an index of LV diastolic dysfunction and the BNP levels were significantly higher in patients with the distal-dominant form.

During the follow-up period, there were no HCM-related cardiovascular deaths among the 51 patients with the pure-apical form, whereas there were 2 such deaths among the 29 patients with the distal-dominant form. The frequency of cardiovascular events (cardiovascular deaths and major morbid events) was significantly higher in patients with the distal-dominant form (1 sudden death, 1 heart failure-death, 2 hospitalizations for heart failure). HCM in the pure-apical form is generally associated with a benign clinical manifestation (only 1 stroke admission). On the other hand, patients with the distal-dominant form had a more symptomatic and worse clinical course, more closely resembling the clinical manifestation of patients with typical HCM. Among the previous investigations of apical HCM, Ericksson et al[11] presented the largest number of patients (105) with apical HCM who were divided into those with the "pure form"

(isolated asymmetric apical hypertrophy) and those with the "mixed form" (with coexisting IVS hypertrophy), using morphologic criteria mainly based on echocardiography. They found no difference between those 2 subtypes with regard to long-term morbid cardiovascular events. The difference in the results of their study and ours may be related to the different definitions of morbidities, the low prevalence of the "mixed form" in their cohort, and the fact that their study population was younger than ours.

However, despite the benign clinical manifestation, patients with the pure-apical form need to be followed up regularly because of the high incidence of AF. The incidence of AF was not low in either the pure-apical or distal-dominant groups compared with that in a whole HCM cohort reported by Olivotto et al (incidence, 2%/year), although our cohort of apical phenotype was older than theirs.[26] The incidence of AF in our cohort was much higher than that in community-dwelling older people (the Kahoku Longitudinal Aging Study, data available upon request). Furthermore, the fact that 4 of 5 patients with the apical phenotype (pure-apical form and distal-dominant form) presented with AF before their cardiovascular events indicates that more careful management (including anticoagulation therapy) is needed for patients with AF. In whole cohort of HCM, AF is known as an important prognostic feature for cardiovascular mortality, stroke, and severe functional disability.[26,27] The results of our study indicate that even in patients with the apical phenotype, in whom complications are considered infrequent, AF seems to be a key determinant of clinical deterioration.

From the longitudinal point of view, some patients with the apical phenotype, including both forms, showed progression and extension of hypertrophy. Although the incidence of familial HCM is relatively high in patients with the distal-dominant form compared with those with the pure-apical form, it is important to recognize young patients with the apical phenotype as the initial manifestation of typical HCM.

Study Limitations

The average follow-up period was about 5 years, and further studies on the outcome and prognosis in patients with the apical phenotype in terms of comparing the 2 forms are needed. Although we found a low frequency of proven familial HCM in the pure-apical form group, genetic screening was not performed in the present study. Several studies have shown that mutations in sarcomere genes, such as the cardiac troponin T, troponin I, cardiac actin, and essential myosin light chain genes, are associated with apical hypertrophy.[28–34] Therefore, it is important to further perform mutation analysis to clarify the genetic difference between the pure-apical and distal-dominant forms.

Conclusions

It is better to clinically distinguish the phenotypes of HCM because patients with the distal-dominant form are significantly more symptomatic and have more cardiovascular events than do patients with the pure-apical form. However, AF is not uncommon in both groups, and careful management is needed once AF has occurred.

Acknowledgments

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Disclosures

None of the authors has a conflict of interest to disclose in connection with this manuscript.

References

1. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med* 1997; **336:** 775–785.
2. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003; **42:** 1687–1713.
3. Maron BJ. Hypertrophic cardiomyopathy: A systematic review. *JAMA* 2002; **287:** 1308–1320.
4. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet* 2004; **363:** 1881–1891.
5. Motoyasu M, Kurita T, Onishi K, Uemura S, Tanigawa T, Okinaka T, et al. Correlation between late gadolinium enhancement and diastolic function in hypertrophic cardiomyopathy assessed by magnetic resonance imaging. *Circ J* 2008; **72:** 378–383.
6. Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y. Giant T wave inversion as a manifestation of asymmetrical apical hypertrophy (AAH) of the left ventricle: Echocardiographic and ultrasono-cardiotomographic study. *Jpn Heart J* 1976; **17:** 611–629.
7. Yamaguchi H, Ishimura T, Nishiyama S, Nagasaki F, Nakanishi S, Takatsu F, et al. Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): Ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol* 1979; **44:** 401–412.
8. Koga Y, Katoh A, Matsuyama K, Ikeda H, Hiyamuta K, Toshima H. Disappearance of giant negative T waves in patients with the Japanese form of apical hypertrophy. *J Am Coll Cardiol* 1995; **26:** 1672–1678.
9. Suzuki J, Watanabe F, Takenaka K, Amano K, Amano W, Igarashi T, et al. New subtype of apical hypertrophic cardiomyopathy identified with nuclear magnetic imaging as an underlying cause of markedly inverted T waves. *J Am Coll Cardiol* 1993; **22:** 1175–1181.
10. Koga Y, Nohara M, Miyazaki Y, Toshima H. Two forms of apical hypertrophic cardiomyopathy: Japanese and Western forms. *In:* Toshima H, Maron BJ, editors. Cardiomyopathy updated. 2: Hypertrophic cardiomyopathy. Tokyo, Japan: University of Tokyo Press; 1988; 293–308.
11. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002; **39:** 638–645.
12. Kitaoka H, Doi Y, Casey SA, Hitomi N, Furuno T, Maron BJ. Comparison of prevalence of apical hypertrophic cardiomyopathy in Japan and the United States. *Am J Cardiol* 2003; **92:** 1183–1186.
13. Doi Y, Kitaoka H, Hitomi N, Yamasaki N, Matsumura Y, Furuno T, et al. Hypertrophic cardiomyopathy in Japan: Clinical, morphologic and genetic expression. *In:* Maron BJ, editor. Diagnosis and management of hypertrophic cardiomyopathy. Malden, MA: Blackwell/Futura; 2004; 185–194.
14. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: A two-dimensional echocardiographic study. *J Am Coll Cardiol* 1983; **2:** 437–444.
15. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: A wide angle, two dimensional echocardiographic study of 125 patients. *Am J Cardiol* 1981; **48:** 418–428.
16. Nagueh SF, Lakkis NM, Middleton KJ, Spencer WH 3rd, Zoghbi WA, Quinones MA. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. *Circulation* 1999; **99:** 254–261.
17. Efthimiadis GK, Giannakoulas G, Parcharidou DG, Karvounis HI, Mochlas ST, Styliadis IH, et al. Clinical significance of tissue Doppler imaging in patients with hypertrophic cardiomyopathy. *Circ J* 2007; **71:** 897–903.
18. Maron BJ, Bonow RO, Seshagiri TNR, Roberts WC, Epstein SE. Hypertrophic cardiomyopathy with ventricular septal hypertrophy localized to the apical region of the left ventricle (apical hypertrophic cardiomyopathy). *Am J Cardiol* 1982; **49:** 1838–1848.
19. Vacek JL, Davis WR, Bellinger RL, McKiernan TL. Apical hypertrophic cardiomyopathy in American patients. *Am Heart J* 1984; **108:** 1501–1506.
20. Abinader EG, Rauchfleisch S, Naschits J. Hypertrophic apical cardiomyopathy: A subtype of hypertrophic cardiomyopathy. *Israel J Med*

Sci 1982; **18:** 1005–1009.
21. Keren G, Belhassen B, Sherez J, Miller HI, Megidish R, Berenfeld D, et al. Apical hypertrophic cardiomyopathy: Evaluation by noninvasive and invasive technique in 23 patients. *Circulation* 1985; **71:** 45–56.
22. Louie ER, Maron BJ. Apical hypertrophic cardiomyopathy: Clinical and two-dimensional echocardiographic assessment. *Ann Intern Med* 1987; **106:** 663–670.
23. Webb JG, Sasson Z, Rakowski H, Liu P, Wigle ED. Apical hypertrophic cardiomyopathy: Clinical follow-up and diagnostic correlates. *J Am Coll Cardiol* 1990; **15:** 83–90.
24. Chikamori T, Doi YL, Akizawa M, Yonezawa Y, Ozawa T, McKenna WJ. Comparison of clinical, morphological, and prognostic feature in hypertrophic cardiomyopathy between Japanese and Western patients. *Clin Cardiol* 1992; **15:** 833–837.
25. Choi EY, Rim SJ, Ha JW, Kim YJ, Lee SC, Kang DH, et al. Phenotypic spectrum and clinical characteristics of apical hypertrophic cardiomyopathy: Multicenter echo-Doppler study. *Cardiology* 2008; **110:** 53–61.
26. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001; **104:** 2517–2524.
27. Doi Y, Kitaoka H. Hypertrophic cardiomyopathy in the elderly: Significance of atrial fibrillation. *J Cardiol* 2001; **37:** 133–138.
28. Kimura A, Harada H, Park JE, Nishi H, Satoh M, Takahishi M, et al. Mutations in the cardiac troponin I gene associated with hypertrophic cardiomyopathy. *Nat Genet* 1997; **16:** 379–382.
29. Anan R, Shono H, Kisanuki A, Arima S, Nakao S, Tanaka H. Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis. *Circulation* 1998; **98:** 391–397.
30. Mogensen J, Murphy RT, Kubo T, Bahl A, Moon JC, Klansen IC, et al. Frequency and clinical expression of cardiac troponin I mutations in 748 consecutive families with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004; **44:** 2315–2325.
31. Olson TM, Doan TP, Kishimoto NY, Whitby FG, Ackerman MJ, Fananapazir L. Inherited and de novo mutations in the cardiac actin gene cause hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2000; **32:** 1687–1694.
32. Poetter K, Jiang H, Hassanzadeh S, Master SR, Chanq A, Dalakas MC, et al. Mutations in either the essential or regulatory light chains of myosin are associated with a rare myopathy in human heart and skeletal muscle. *Nat Genet* 1006; **13:** 63–69.
33. Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrid M, Ho CY, et al. Gene mutations in apical hypertrophic cardiomyopathy *Circulation* 2005; **112:** 2805–2811.
34. Monserrat L, Hermida-Prieto M, Fernandez X, Rodriguez I, Dumont C, Cazon L, et al. Mutations in the alpha-cardiac gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects. *Eur Heart J* 2007; **28:** 1953–1961.

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REVIEW ARTICLE

Hypertrophic cardiomyopathy in the elderly

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Hypertrophic cardiomyopathy (HCM) is a relatively common genetic cardiac disorder with heterogeneous morphological, functional and clinical features. Although the risk of sudden death and incapacitating symptoms in young patients has been focused upon, the disease has been found with increasing frequency in elderly patients. However, there have been few studies on clinical features of HCM in the elderly. We established a cardiomyopathy registration study in Kochi Prefecture, which is one of the most aged communities in Japan, to provide detailed descriptions of the clinical features of HCM in a community-based patient cohort. The unselected regional HCM population consisted largely of elderly patients (70% of the study cohort being ≥60 years of age at registration), although HCM has been regarded largely as a disease of the young. Cardiac hypertrophy that becomes clinically apparent late in life can be a genetic disorder, and mutations in the cardiac myosin-binding protein C gene are the most common cause of late-onset or elderly HCM. In the morphological features, sarcomere gene defects seem to have a predilection for a crescent-shaped left ventricular cavity with reversed septal curvature even in elderly patients, although an ovoid left ventricular shape was frequently seen in elderly patients in previous clinical studies on morphological characteristics of HCM. In middle-aged or elderly patients with HCM, heart failure and embolic events, which were strongly associated with atrial fibrillation, were very important. It is important to manage HCM patients from the standpoint of longitudinal evolution in order to prevent those clinical complications. **Geriatr Gerontol Int 2010; 10: 9–16.**

Keywords: atrial fibrillation, embolism, heart failure, hypertrophic cardiomyopathy, lifelong remodeling.

Introduction

Hypertrophic cardiomyopathy (HCM), a relatively common genetic cardiac disorder, is clinically defined by the presence of left ventricular hypertrophy (LVH) in the absence of another cardiac or systemic disease capable of producing that magnitude of hypertrophy and it has heterogeneous morphological, functional and clinical features.[1–3] The natural history of HCM varies from an asymptomatic and benign course to sudden premature death. Since the initial description of HCM in 1958, death resulting from HCM, particularly when sudden, had been reported to be largely confined to young persons. However, most HCM patients avoid suffering from sudden death and survive with the disease for long periods. Furthermore, there have been several reports of LVH of HCM occurring after middle age in a significant subset of patients.[4,5] In fact, the disease has been found with increasing frequency in elderly patients. In this review, clinical features of HCM, particularly focusing on elderly patients, are summarized largely based on the data from unselected regional cohort.

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Regional cohort of HCM: Kochi RYOMA study

Previous reports on prognosis from major tertiary HCM centers with highly selected referral patterns skewed

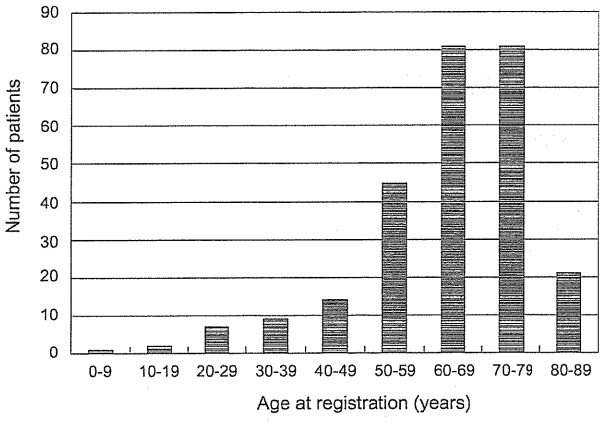

Figure 1 Distribution of age at registration in patients with hypertrophic cardiomyopathy at Kochi RYOMA study. Reproduced from Kubo *et al.*,[13] with permission from The Japanese Circulation Society.

toward high-risk patients.[6–8] Recent observations in community-based and predominantly unselected patient cohorts in the USA and Europe suggest a more favorable prognosis than that suggested by results of previous studies.[9–12] However, there have been few studies on clinical features of HCM in a community-based and unselected patient cohort in Japan. Therefore, we established the Kochi Cardiomyopathy Network, named the Kochi RYOMA (Registry of Myocardial Diseases) study, to provide detailed descriptions of the clinical features of HCM in an unselected regional Japanese population.[13]

This network consists of nine hospitals serving as primary, secondary and tertiary referral medical centers for cardiovascular patients in Kochi Prefecture, Japan with 800 000 inhabitants. A total of 261 patients (173 men and 88 women) with a diagnosis of HCM were registered between 2004 and 2008. The ages at registration and at diagnosis were 64 ± 14 (range: 9–88) and 57 ± 15 (range: 6–87) years, respectively (Fig. 1).[13] The ages of 183 (70%) of those patients at registration were 60 years or older. This age distribution of patients in the present study is probably due to the fact that Kochi Prefecture, where our study was performed, is located far from urban areas and is one of the most aged communities in Japan. We think that, at least in the Japanese rural region, many patients with this cardiomyopathy in the daily clinics are middle-aged or elderly despite HCM being regarded as a genetic disorder.

Gene abnormalities in HCM of the elderly

Although HCM was considered "idiopathic", it was also recognized as a familial disease in the late 1950s and early 1960s. Approximately half of the cases of HCM were familial. Over the past 15 years, considerable progress in molecular genetics has been made and an understanding of the disease has been achieved. Since a mutation in the β-myosin heavy chain gene was first identified as a cause of familial HCM, at least eight genes that encode sarcomere contractile proteins have been reported in individuals and families with HCM: β-cardiac myosin heavy chain (*MYH7*); cardiac myosin-binding protein C (*MYBPC3*); cardiac troponin T (*TNNT2*); cardiac troponin I (*TNNI3*); α-tropomyosin (*TPM1*), and, more rarely, the essential or regulatory myosin light chains (*MYL3*, *MYL2*); and cardiac actin (*ACTC*).[14,15] Although HCM is usually detected by early adulthood, several recent reports have shown that late-onset HCM can also be caused by sarcomere protein gene mutations.[4] Seidman's group reported that they analyzed 31 patients with late-onset HCM recruited with clinical expression or diagnosis made for the first time after 40 years of age (mean diagnostic age: 62.8 ± 10.8 years) and that HCM in seven of those patients was considered to be caused by sarcomere protein gene mutations (four mutations in *MYBPC3*, two mutations in *TNNI3* and one mutation in α-cardiac myosin heavy chain gene).[16] Anan *et al.* reported the mutations in Japanese patients with sporadic HCM onset after 40 years of age and four missense mutations in *MYBPC3* and one missense mutation in *MYH7* were identified in five of 41 patients.[17]

In our Kochi cohort, we performed genetic analysis in 34 unrelated HCM patients aged 60 years or older at diagnosis (five sarcomere protein genes: *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*) and six (18%) of those patients had mutations (two patients were known to have familial HCM at the time of genetic testing, and after detecting mutations, subsequent family screening revealed two other patients with familial HCM). All mutations were in *MYBPC3* (three mutations in six unrelated patients: two frame-shift deletion mutations [S593fs and R945fs] and one nonsense mutation [S297X]). Based on the results of previous studies and our genetic study, cardiac hypertrophy that becomes clinically apparent late in life can be a genetic disorder and mutations in the cardiac myosin-binding protein C gene are the most common cause of delayed expression of hypertrophy (late-onset HCM).

Morphological characteristics of HCM in the elderly

Although advances in genetic testing have enabled identification of a variety of mutations in genes encoding sarcomere proteins as mentioned above, the prevalence of genetic defects in elderly patients with HCM is relatively low.[4,5,16–19] This raises uncertainty as to whether HCM in the elderly is the same genetic disease as that in young patients or a distinct entity with overlapping morphological phenotypes. Several clinical and

Table 1 Comparison of the echocardiographic findings of elderly and young patients with *MYBPC3* mutations

	Elderly ($n = 8$)	Young ($n = 19$)	P
Ovoid shaped-LV cavity with normal septal curvature, *n* (%)	2 (25%)	1 (5%)	NS
Crescent shaped-LV cavity with reversal curvature, *n* (%)	6 (75%)	18 (95%)	NS
Proximal septal bulge, *n* (%)	0 (0%)	0 (0%)	NS
Right ventricular hypertrophy, *n* (%)	1 (13%)	9 (47%)	0.2
Mitral annular calcification, *n* (%)	3 (38%)	0 (0%)	0.02
Mitral regurgitation, *n* (%)	1 (25%)	0 (0%)	0.04
LV end-diastolic diameter, mm	46 ± 7	42 ± 5	0.12
LV end-systolic diameter, mm	30 ± 7	25 ± 4	0.03
Fractional shortening, %	37 ± 7	41 ± 6	0.07
Interventricular septal thickness, mm	17 ± 3	22 ± 5	0.02
Posterior wall thickness, mm	10 ± 2	11 ± 3	NS
Maximum LV wall thickness, mm	18 ± 2	24 ± 6	0.008
Wigle score	5.7 ± 1.5	7.6 ± 1.6	0.005
Left atrial diameter, mm	49 ± 10	40 ± 6	0.008

Reproduced from Hirota *et al.*,[25] with permission from The Japanese Circulation Society. LV, left ventricular; *MYBPC3*, cardiac myosin binding protein C gene; NS, not significant.

morphological characteristics of HCM in elderly patients, including higher prevalences of an ovoid LV shape, proximal septal bulge and mitral annular calcification than those in young patients, have been reported.[20–24] However, those studies were carried out before genetic testing became available. It is possible that LVH of heterogeneous cause or age-related morphological changes were included. Therefore, uncertainty remains as to whether the previously reported morphological characteristics are indeed common in elderly patients with HCM caused by sarcomere gene mutations. We reevaluated the morphological features of HCM in elderly patients with mutations in the cardiac myosin-binding protein C gene (*MYBPC3*), the most common genetic cause of HCM in the elderly.[25] Among 65 patients who were enrolled for clinical evaluation and genetic testing at Kochi Medical School, 27 patients with HCM caused by mutations in *MYBPC3* were evaluated. Individuals with left ventricular (LV) systolic dysfunction (dilated phase of HCM) or apical HCM were excluded because they were not suitable for analysis of LV morphology. Patients were divided into an elderly group (≥65 years of age, $n = 8$ [mean age, 73 ± 7; range 65–83 years]) and a young group (<65 years of age, $n = 19$ [mean age, 45 ± 11; range 28–61 years]). The echocardiographic findings in the two groups are shown in Table 1. LV hypertrophy was milder in the elderly group than in the young group for maximum LV wall thickness and Wigle score. LV end-systolic diameter and left atrial size were larger in the elderly patients than in the young patients. Furthermore, right ventricular hypertrophy tended to be seen in the young patients and mitral annular calcification was common in the elderly patients. On the other hand, a distinct crescent-shaped

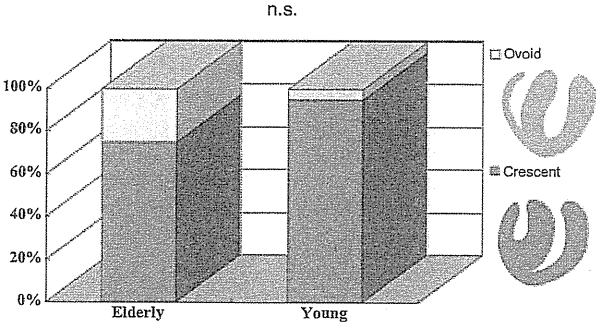

Figure 2 Comparison of left ventricular shapes in young and elderly patients with hypertrophic cardiomyopathy. Reproduced from Hirota *et al.*,[25] with permission from The Japanese Circulation Society.

LV cavity, with reversed septal curvature, was prominent in both groups (Fig. 2). Also, none of the elderly patients showed a proximal septal bulge. The results of our study are distinctly different from those of studies carried out before gene testing became available. Although the morphological features in patients with HCM caused by other sarcomere gene mutations are unresolved, a crescent-shaped LV in elderly patients with LVH suggests a genetic disorder caused by mutations in *MYBPC3* rather than hypertensive hypertrophy or age-related changes. The Mayo Clinic group reported that genetic analysis of 382 unrelated HCM patients was performed and 143 patients had HCM-associated mutation.[26] They found that 104 of 132 patients (79%) with reverse curvature HCM, morphology similar to a crescent-shaped LV, were genotype-positive, whereas only 15 of 181 patients (8%) with sigmoid septal HCM were genotype-positive.[26] The major conclusions to be