Review

The Past and Present Status of Clinical Hyperthermia in Japan : a Survey in 2004 using a Questionnaire

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Abstract : Clinical research in hyperthermic oncology began in 1978, when the research group chaired by Prof. T. Sugahara, supported by a grant from the Ministry of Education, played an important part. Six years later, the first annual meeting of the Japanese Society of Hyperthermic Oncology (JSHO) was held in Kyoto, and the 23rd meeting was held in Nara in 2006. Over this period, the number of members as well as the number of scientific papers presented have decreased. However, new technologies such as immuno-stimulation, high temperature ablation, and mild hyperthermia have been introduced into clinics. The health insurance control committee of the JSHO conducted a survey on the clinical applications of hyperthermia. Data obtained through the use of questionnaires have been used to present the state of hyperthermic treatment in the major hospitals in Japan. An outline of the patients and diseases treated with hyperthermia, heating conditions including combination therapy, and clinical outcomes were summarized in this study. From the viewpoint of fiscal responsibility at each hospital, the difference between income and expenses for hyperthermic therapy is something which cannot be ignored. Further analysis of survey data and additional survey studies might be essential to resolve this problem.

Key Words : hyperthermia, RF capacitive heating, questionnaire survey, local response

Introduction

Clinical research in hyperthermic oncology was started by the Japanese Hyperthermic Study Group (JHSG) in 1978. A research group chaired by Prof. T. Sugahara, supported by a grant from the Ministry of Education, played an important part in the establishment of JHSG. The first scientific meeting was held in Osaka, and was attended by 50 researchers, and 17 papers were presented[1)]. The first presentations dealt mainly with problems dealing with heating of the human body and the biological effects obtained using various heating procedures. The little clinical data presented and discussed were

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in the field of hyperthermia using perfusion with hot water for the treatment of carcinoma of the urinary bladder. Six years later, in 1984, the Japanese Society of Hyperthermic Oncology (JSHO) was established[1-3] (Table I). Since then, the JSHO has made substantial progress when compared to the North American Hyperthermia Society (NAHS) and the European Society for Hyperthermic Oncology

Table I. History of the annual meeting for the presentation of research in hyperthermia in Japan

No.	Year	Location	Chairman
Hyperthermic Study Group : Annual Meeting			
1	1978	Osaka	Sugahara T.
2	1979	Osaka	Sugahara T.
3	1980	Kyoto	Onoyama Y.
4	1981	Tokyo	Egawa S. & Saito M.
5	1982	Nagoya	Nakamura W. & Amemiya Y.
6	1983	Tokyo	Matsuda T. & Kikuchi M.
Japanese Society of Hyperthermic Oncology : Annual Meeting			
1	1984	Kyoto	Sugahara T. (JSHO established)
2	1985	Tokyo	Egawa S.
3	1986	Osaka	Onoyama Y.
4	1987	Yonago	Koga N.
5	1988	Kyoto	Sugahara T. (Joint Conference with the 5th ICHO)
6	1989	Tokyo	Saito M.
7	1990	Okayama	Sekiba K.
8	1991	Tokyo	Kamata R.
9	1992	Kanazawa	Hisazumi H.
10	1993	Osaka	Shimoyama T.
11	1994	Osaka	Tanaka Y.
12	1995	Tokyo	Kanai H.
13	1996	Fukuoka	Sugimachi K. (1st Congress of ASHO)
14	1997	Kyoto	Kondo M.
15	1998	Tokyo	Tanaka Y. (2nd Congress of ASHO)
16	1999	Osaka	Kano E.
17	2000*	Niigata	Tanaka R.
18	2001	Tokyo	Takahashi T.
19	2002**	Nagoya	Ueda K.
20	2003	Fukuoka	Masuda K.
21	2004	Kyoto	Yoshikawa T.
22	2005	Okayama	Kawasaki S.
23	2006	Nara	Ohnishi T. (4th Congress of ASHO)

*The 8th ICHO was held in Kyon-ju, Korea, in 2000.

**The 3rd ASHO was held in Zhengzhou, Henan, China, in 2002.

(ESHO). The JSHO was organized by Professor Tsutomu Sugahara, from Kyoto University, Kyoto. He was succeeded in 1991 by Tadayoshi Matsuda, of the Tama-Nambu Regional Hospital, Tokyo. In 1995, Professor Yoshiaki Tanaka, from Nihon University School of Medicine, Tokyo, became president, and he was succeeded by Professor Makoto Kikuchi, of the National Defense Medical College, from 1998 to 2002. The current president, Professor Takeo Ohnishi, of Nara Medical University, became president in 2003.

Membership and Organization of the JSHO

In March, 1998 there were 918 members in the JSHO. This group was comprised of 697 clinical oncologists which included specialists in radiation oncology and radiology (281); surgery (169); internal medicine (85); urology (38); neurosurgery (36); oral and maxillo-facial surgery (27); gynecology (12); *etc.* Two hundred and twenty one members came from other disciplines; physics and engineering (94); biology (59); and associated medical and radiological technicians, nurses and others[3] (68). In North America and Europe, radiation oncologists constitute more than 70% of the membership of the Hyperthermic Societies. Current JSHO membership has decreased, and includes 493 clinical oncologists (72%), 104 basic scientists (15%), and 89 members from other disciplines (13%) (Table II).

Scientific papers presented at the Annual Meeting of the JSHO

To analyze the effect of the JSHO's efforts, the numbers of scientific papers presented at the annual meetings was analyzed. This examination shows a gradual increase in the number of papers presented at each meeting from 1984 through 1988, when the 5th Congress of the International Society for

Table II. Number of JSHO members in different subspecialty fields in 2004

No.	Department	Number	Number (%)
1	Radiation Oncology & Radiology	205	493 (72)
2	Surgery	129	
3	Internal Medicine	54	
4	Urology	20	
5	Neurosurgery	18	
6	Oto-rhino-laryngology/Oral and maxillofacial Surgery/Dentistry	5/15/10	
7	Gynecology	7	
8	Clinics (Others)	30	
9	Physical Science and Engineering	68	104 (15)
10	Biology	14	
11	Other Basic Science in Medicine	22	
12	Radiological Technology	44	89 (13)
13	Others	45	
Total		686	(100)

Hyperthermic Oncology (ISHO) was held and 222 papers were presented[4]. After that, the number decreased gradually to an average of 120 papers a year. The year of 1998 was special since the combined 2nd Congress of the Asian Society of Hyperthermia Oncology (ASHO) and the JSHO was held in Tokyo[5] (Fig. 1).

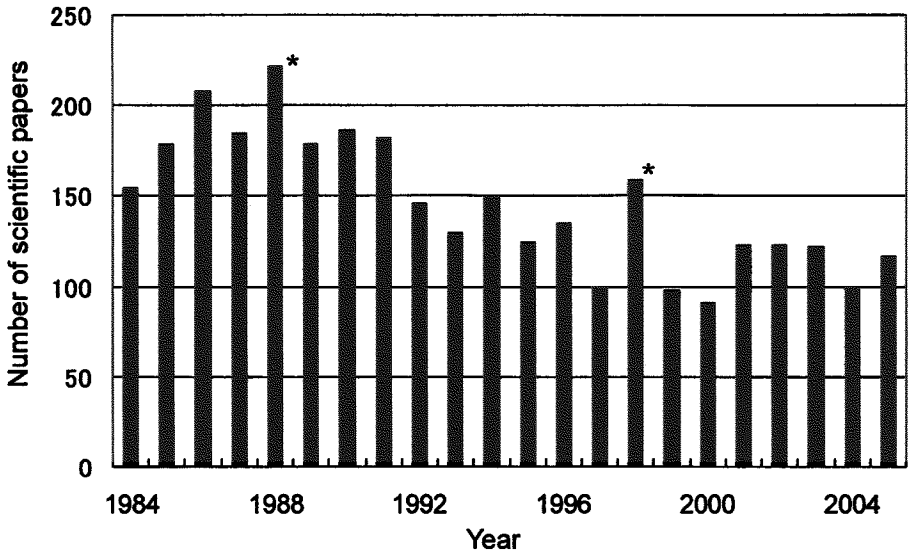

Fig. 1. Number of scientific papers presented at the annual meeting of the JSHO from the 1st Meeting in 1984 through the 22nd Meeting in 2005. (*) The 5th meeting in 1988, Kyoto, and the 15th meeting in 1998, Tokyo, were held in conjunction with the 5th ICHO and the 2nd ASHO, respectively.

Board Certification

In order to promote the effectiveness, quality, and safety of hyperthermic treatment in clinical practice, the JSHO established a board certification for hyperthermic oncology in 1996 both for physicians and researchers, and for associated medical staff, including radiotherapy technicians and nurses. A certification was also established for institutions. The JSHO also founded educational refresher courses in conjunction with district scientific meetings for the management and establishment of board certification. This is an effective approach leading to the increase of quality assurance in hyperthermic treatment in clinical applications.

Clinical applications

A nation-wide survey revealed that radiofrequency (RF) capacitive heating equipment was the most common choice for the treatment of deep-seated tumors, mainly using the Thermox 500/1000 (Omron Co., Ltd., Kyoto, Japan) and the Thermotron-RF8 (Yamamoto Vinita Co., Ltd., Osaka, Japan) instruments. Initially, hyperthermia was used in conjunction with radiation therapy in about 60% of the patients, with chemotherapy in 25%, and with chemo-radiotherapy in 15%. At this time, hyperthermia was usually applied to 1) locally advanced tumors, 2) radio-resistant tumors, 3) recurrent tumors, 4) accessible tumors which could be easily heated, and 5) others not suitable for management with radiation

alone[6]. In April 1990, the Japanese Government approved the use of health insurance to cover the costs of treatment by hyperthermia when it was limited to the application of an electromagnetic field, provided that it be used in combination with radiotherapy. Since then, there has been a remarkable increase in the frequency of clinical applications of hyperthermia in cancer treatments. In April 1996, hyperthermia applied with equipment using an electromagnetic field was approved for clinical uses other than combination with radiotherapy. Since then, clinical applications have been expanded to cover any tumors treatable with hyperthermia. In the United States and Europe, most clinical trials used microwave heating of superficial tumors. In Japan, research in the field of hyperthermia has mainly focused on RF capacitive heating for the treatment of deep-seated tumors. Based on the findings published during the initial ten years, it is possible to chart the effectiveness and progress of treatment modalities involving hyperthermia for the following diseases : 1) thermo-radiotherapy for metastasis to the cervical lymphnode[7], locally advanced carcinoma and/or postoperative recurrent tumors of the breast[8], lung[9-12] (especially treatments of superior sulcus tumors), rectum[13,14], uterine cervix[15,16] and soft tissue sarcoma[17,18], 2) thermo-chemotherapy for lung cancer with carcinomatous dissemination to the pleura[19], peritonitis carcinomatosa[20-22], hepatocellular carcinoma[23,24], and vaginal carcinoma[25], and[3] thermo-chemo-radiotherapy for locally advanced head and neck cancer[26] and carcinoma of the breast[8,27], esophagus[28,29], malignant mesothelioma[30,31], extrahepatic biliary system[32], pancreas[13,33], uterine cervix[16] and urinary bladder[34].

Results of a questionnaire survey of clinical hyperthermia in Japan

The health insurance control committee of the JSHO conducted a survey on the clinical applications of hyperthermia in Japan. Data were obtained from questionnaires distributed from January, 2003 through December, 2004 to major medical centers, in which hyperthermic equipment using an electromagnetic field was installed and used for the treatment of cancer patients. A total of 25 institutes were registered for this study. The hyperthermic equipment consisted of 23 units of the Thermotron-RF8, one unit of the Thermotron pro-eight, and one unit of the Thermox 500, all of which are radiofrequency (RF) capacitive heating devices. A total of 1,151 patients had been treated with hyperthermia each year in these 25 institutes. The number of patients treated per institute ranged from 5 to 205 patients per year (average 41.3 patients ; median 18 patients) and the number of sessions per patient from 1.3 through 13.8 sessions (average of 10.4+/−9.5 sessions). The treatment period per patient ranged from less than one month to more than 6 months (average 2.1+/−1.2 months) with about half of the patients (48.4%) treated for less than one month with 4.0+/−2.2 hyperthermia sessions (Table III). The abdomen was the area most frequently treated with hyperthermia (37.3%) followed by the pelvic region (30.6%), thorax (19.7%), head & neck (7.3%), and bone & soft tissue (5.1%) (Table IV). Chemotherapy, radiotherapy, and chemo-radiotherapy were applied in combination with hyperthermia, where chemotherapy was the most frequent modality (33.9%) followed by radiotherapy (25.4%), chemo-radiotherapy (23.0%) and hyperthermia alone (17.6%) (Table V). Local responses were analyzed by groupings of combination therapy with chemotherapy and/or radiotherapy. The data were obtained from subjective impressions of physicians in which "excellent" meant that nearly all tumors and symptoms had disappeared, including discomfort and pain ; "good" meant partial regression of the

Table III. Distribution of hyperthermic treatments (HT) : treatment period, number of patients, and treatment sessions

	Treatment period (months)					
	<1	1=<, <2	2=<, <3	3=<, <6	6=<, <12	12=<
Number of patients (%)	477 (48.4)	192 (19.5)	103 (10.4)	114 (11.6)	75 (7.6)	25 (2.5)
Number of HT sessions (S.D.)	4.0 (2.2)	8.7 (5.5)	13.5 (8.5)	19.4 (12.4)	42.5 (39.7)	47.3 (21.5)

Table IV. Distribution of patients treated with hyperthermia (HT) : site of treatment lesions

	Head & neck	Thorax	Abdomen	Pelvic region	Bone & soft tissue
Total number of patients	84 (7.3%)	225 (19.7%)	427 (37.3%)	350 (30.6%)	58 (5.1%)
Average number of HT sessions	10.7±8.2	11.1±12.4	11.7±10.3	8.3±4.7	7.4±4.8
Average HT treatment period (months)	2.3±2.0	2.1±1.3	3.5±5.7	1.9±1.5	1.9±1.8

Table V. Distribution of treatment modalities combined with hyperthermia (HT)

	CT	CT+RT	RT	HT alone
Number of patients	360 (33.9%)	244 (23.0%)	270 (25.4%)	187 (17.6%)
Number of HT sessions	13.4±11.8	11.9±12.6	6.2±5.4	10.1±6.6
Treatment period (months)	2.6±1.6	3.5±4.2	1.2±0.6	2.2±1.5

CT : chemotherapy, RT : radiotherapy

Table VI. Local responses of different treatment modalities in combination with hyperthermia (HT)

	CT	CT+RT	RT	HT alone	Total
Excellent	54 (15.0)	92 (37.6)	134 (49.5)	14 (7.5)	294 (27.7)
Good	156 (43.4)	89 (36.5)	98 (36.5)	89 (47.6)	432 (40.7)
No response	150 (41.6)	63 (25.9)	38 (14.0)	84 (44.9)	335 (31.6)
Total	360	244	270	187	1,061

( ) : %, CT : chemotherapy, RT : radiotherapy

tumors or clinical symptoms ; and "no response" meant non- or minimal regression and no substantial changes. The best effects were obtained with hyperthermia combined with radiotherapy in 134 out of 270 cases (49.6%) followed by chemo-radiotherapy in 92 out of 244 cases (37.7%), chemotherapy in 54 out of 360 cases (15.0%) and hyperthermia alone in 14 out of 187 cases (7.5%) (Fig. 2).

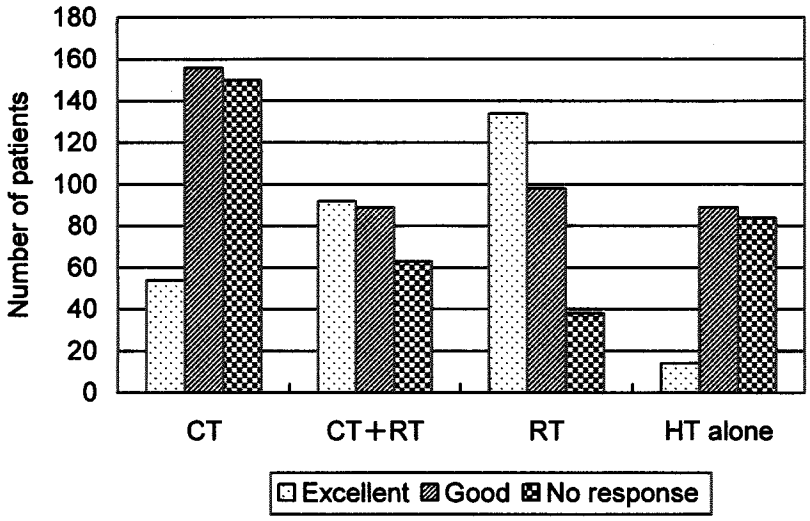

Fig. 2. Local responses analyzed by treatment modalities in combination with hyperthermia (HT). The evaluations were categorized using a scale described in the text. CT : chemotherapy, RT : radiotherapy.

Discussion

In Japan, research work with hyperthermia began in 1978 with the establishment of the Japanese Hyperthermia Study Group (JHSG). Six years later, in 1984, the JSHO was established with 650 members[1,3]. Since then the JSHO has made remarkable progress in both, the fields of basic science, and in clinical practice[35]. At the same time, RF capacitive heating devices such as the Thermotron-RF8 which is effective for heating over wide regions of the human body became available. In 1990, the Japanese Government approved the use of health insurance to cover hyperthermia treatment limited to the application of an electromagnetic field and in combination with radiotherapy, and these conditions were later changed to either combination with chemotherapy or hyperthermia alone. JSHO membership increased markedly during the initial years, but decreased and has stabilized at a number of about 660[3].

Based on the material presented here, treatment is available for the following malignancies : (1) Locally advanced carcinoma and/or postoperative recurrent tumors of the breast, lung (superior sulcus tumor), rectum, and soft tissue sarcoma in RT-HT. (2) Carcinoma of the esophagus, pancreas, and extrahepatic biliary system in CT-RT-HT. Initially, more than two hundred heating units were installed, but many institutions withdrew from clinical applications of their equipment because of problems encountered during the clinical uses of heating procedures, or because of economic considerations. These problems will probably be manageable in the near future as more scientific data becomes available concerning the clinical benefits of HT in cancer treatments.

In order to develop measures to cope with the problem of low reimbursement costs for the application of hyperthermia, the health insurance control committee of the JSHO conducted a survey of the clinical applications of hyperthermia. Data obtained with questionnaires have shown that the treatment period per patient averaged 2.1 months. The abdomen was most frequently treated with hyperthermia, followed by the pelvic region and the thorax. Chemotherapy, radiotherapy, and chemo-radiotherapy were used frequently in combination with hyperthermia, and the best effects were obtained in combined therapy with radiation, followed by combination therapy with chemo-radiotherapy, combination therapy with chemotherapy, and with hyperthermia alone.

The financial situation of individual hospitals is important, and the difference between the income received and expenses incurred for the application of hyperthermia is something which cannot be ignored. For example, three staff members, or a team involving a doctor, a technician and a nurse are required for the clinical application of hyperthermia with an average duration of about 2 hours for a treatment. In considering personnel expenditures, and the costs of the equipment and expendables used in the application of hyperthermia, it is clear that under the present situation, the hospitals can not recover their costs from the health care system in Japan. Further promotion or education concerning hyperthermia may be necessary to improve this situation, and also to increase the frequency of clinical applications, and improve clinical results from the use of hyperthermia in the treatment of cancer patients.

Acknowledgments

The survey study was performed with co-operation of the health insurance control committee of the JSHO. This study was partially funded by a Grant-in-Aid for Scientific Research (No.18591394) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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International Journal of Cardiology 113 (2006) e26–e29

International Journal of Cardiology

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Letter to the Editor

Successful treatment of primary cardiac B-cell lymphoma: Depiction at multislice computed tomography and magnetic resonance imaging

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Received 12 April 2006; accepted 15 July 2006

Abstract

Primary cardiac malignant lymphomas are extremely rare and the majority of lymphomas are aggressive B-cell lymphomas. We describe a patient with primary cardiac B-cell lymphoma presenting with superior vena caval syndrome and dyspnea. The tumors manifested as hypoechoic immobile masses on echocardiography, poorly enhancing masses on contrast-enhanced multislice computed tomography and iso-intense masses on T1-weighted and hyper-intense masses on T2-weighted magnetic resonance images. Pathologic examination revealed that the mass was consistent with B-cell malignant lymphoma. Systemic chemotherapy together with monoclonal CD 20 antibody treatment was initiated. There was marked regression of the tumor 4 days after the treatment and complete disappearance of the tumor after 8 days after the treatment without episodes of systemic or pulmonary embolism.

Keywords: Primary cardiac lymphoma; Multislice computed tomography; Magnetic resonance imaging; Monoclonal CD 20 antibody

1. Case report

A 77-year-old woman was referred to our hospital for biopsy of her cervical lymphnode. She had had mild degree fever, dyspnea on effort, facial and right arm edema and bilateral cervical lymphadenopathy, which started 2 months earlier. On physical examination, there was a marked dilatation of both jugular veins, and facial and right arm edema. Laboratory examinations revealed that an increase in C-reactive protein (2.9 mg/dl) and lactate dehydrogenase (360 IU/L). The hematologic findings were unremarkable. Human immunodeficiency virus (HIV) was negative. Bone marrow aspiration and biopsy revealed no infiltration of the lymphoma cells. Transthoracic echocardiography showed an immobile, hypoechoic round mass in the right atrium and the left atrium (Fig. 1a). Color Doppler imaging disclosed that the mass obstructed the drainage flow from the superior vena cava into the right atrium (Fig. 1b). Contrast-enhanced multislice computed tomography (MSCT) was performed using a SOMATOM Volume Zoom (Siemens, Erlangen, Germany) with a gantry rotation of 500 ms/rotation and collimation of 3.0 mm. MSCT showed masses which were homogeneous and poorly enhanced (Fig. 2a–d). The right coronary involvement by the right atrial mass was also depicted (Figs. 2a and 1b). The coronal image showed the obstruction of the superior vena cava–right atrium inflow tract (Fig. 2d). Magnetic resonance imaging (MRI) was performed by using an Intera Achieva (1.5 Tesla, Philips Medical Systems, Netherlands). All the images were acquired by using navigator-guided, free-breathing sequences. T1-weighted images (Fig 2e–g) showed homogeneous

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doi:10.1016/j.ijcard.2006.07.090

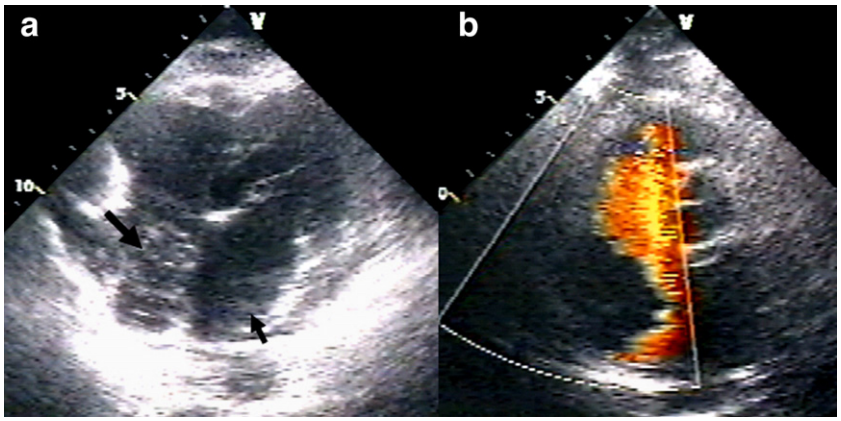

Fig. 1. a: Echocardiography showing relatively hypoechoic masses in the right atrium (large arrow) and in the left atrium (small arrow), b: Color Doppler imaging showing that the mass obstructs the superior vena cava–right atrium inflow tract.

masses (3×3 cm, *x* and *y* axis, respectively) in the right atrium and in the left atrium (7×6×3 cm, *x*, *y* and *z* axis, respectively) with signals equivalent to the myocardium. T2-weighted images (Fig. 2h–j) revealed that the masses were mildly high-intense. A ^{67}Ga scintigraphy showed abnormal uptake in the heart (Fig. 2k,l). Microscopic examination of the biopsy specimen from the right cervical lymphnode showed diffuse proliferation of large atypical lymphoid cells with ovoid hyperchromatic nuclei and prominent nucleoli (Fig. 3a). Immunohistochemical investigations disclosed negative reactivity with anti-keratin, anti-T cell, and positive reactivity with CD 20 (Fig. 3b). Thus, the diagnosis of primary cardiac B-cell malignant lymphoma was confirmed and the patient underwent systemic chemotherapy consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisolone and monoclonal CD 20 antibody (Rituximab) (R-CHOP). Surprisingly, there was marked regression of the tumor 4 days after the initiation of R-CHOP therapy, and almost complete disappearance of the tumor was achieved 8 days after the R-CHOP therapy (Fig. 4). There

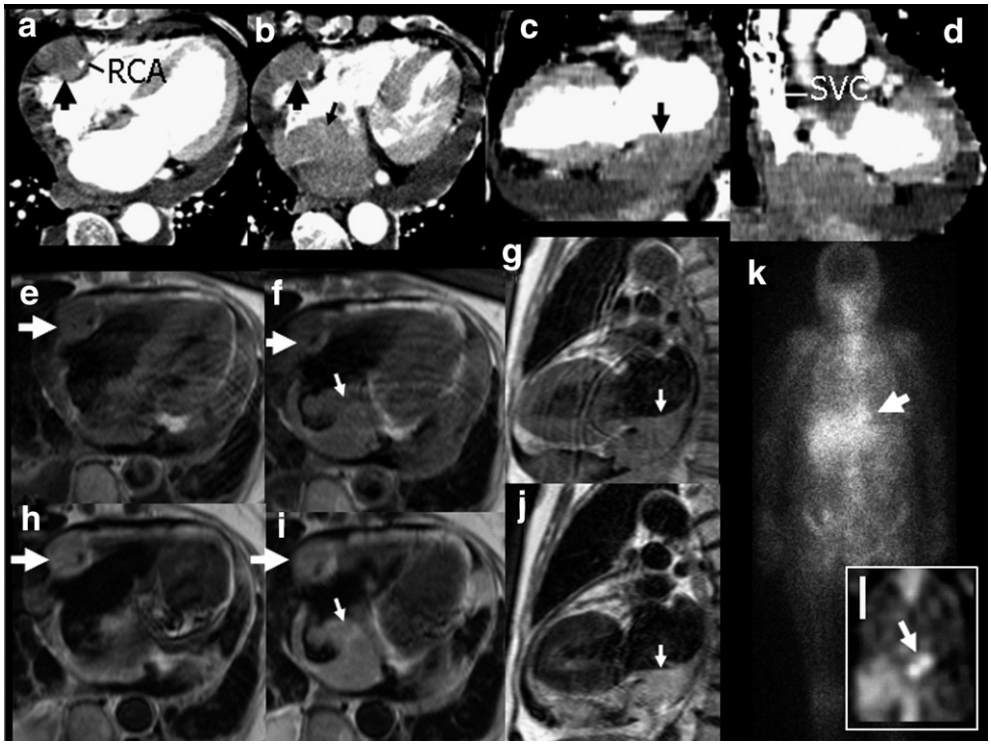

Fig. 2. Contrast-enhanced multislice computed tomographic images on the horizontal axis (a, b) demonstrating non-contrast-enhanced masses in the right atrium (large arrows) which surrounds the right coronary artery (RCA) and in the bottom of the left atrium (small arrow). The long axis image (c) showing the mass in the left atrium (arrow). Coronal image (d) showing obstruction of the superior vena cava (SVC)–right atrium inflow tract by the tumor. T1-weighted magnetic resonance images on the axial (e, f) and long-axis (g) planes showing iso-intensity masses in the right (large arrows) and left atrium (small arrows). The masses are mildly high-intense on T2-weighted images (h–j). Planar (k) and tomographic (l) images of ^{67}Ga scintigram showing high isotope uptake in the heart (arrows).

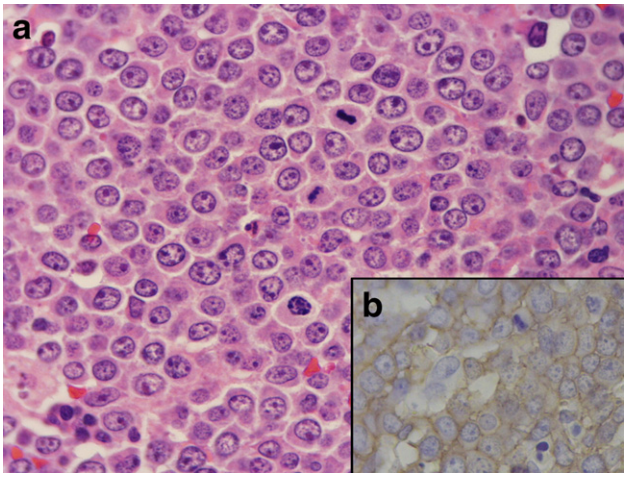

Fig. 3. (a) Histologic section from the cervical lymphnode showing large abnormal cells with irregular nuclei (hematoxylin and eosin stain, ×600) which positively stained for CD 20 antigen (b).

were no major complications such as systemic or pulmonary embolism.

2. Discussion

Primary cardiac lymphoma, defined as a non-Hodgkin's lymphoma involving only the heart and/or pericardium or as a lymphoma with the bulk of the tumor located on the heart is extremely rare in immunocompetent patients, accounting for 1.3% of all cardiac tumors [1]. In the reviewed cases, approximately 80% is a B-cell lymphoma of the diffuse cell type [2,3]. Primary cardiac lymphoma remains asymptomatic until it produces a mass effect when the tumor obstructs cardiac chambers and great vessels, pulmonary or systemic embolization, complete atrioventricular block and cardiac tamponade. Transthoracic echocardiography is the first choice of diagnostic modality for the diagnosis of primary cardiac lymphomas, but because of its limited acoustic window, the extent of the tumor can not be fully evaluated. Contrast-enhanced computed tomography (CT) and MRI have advantages over echocardiography because they provide better contrast resolution and allow simultaneous visualization of the great vessels, heart, pericardium, mediastinum and the lung. Furthermore, CT and MRI may represent information useful for the differential diagnosis of tumors depending on their CT density and/or MR signal intensity characteristics, especially in cardiac lipoma, osteochondrosarcoma and pericardial cysts. Although reports describing CT characteristics of primary cardiac lymphoma are rare, primary cardiac lymphoma is characterized by homogeneous and poorly enhanced mass [4], as was found in our patient. MRI may be even more advantageous to CT because it allows tissue characterization of the tumor. MRI findings on primary cardiac lymphoma are scarce, but homogeneous, iso- or hypointensity on T1-weighted image and relatively hyper-intensity on T2-weighted image have been observed [4,5]. In addition, heterogeneity of the signal intensity on T2-weighted image has been reported to be related with a malignancy grade of lymphoma [6]. Primary cardiac lymphoma, unlike other cardiac malignancies, responds to chemotherapy. In fact, there was almost complete disappearance of the tumor 8 days after the initiation of R-CHOP therapy in our patient without systemic or pulmonary embolism. Thus, accurate diagnosis by CT and MRI, and subsequent early treatment are of utmost importance in the management of patients with suspected primary cardiac lymphoma.

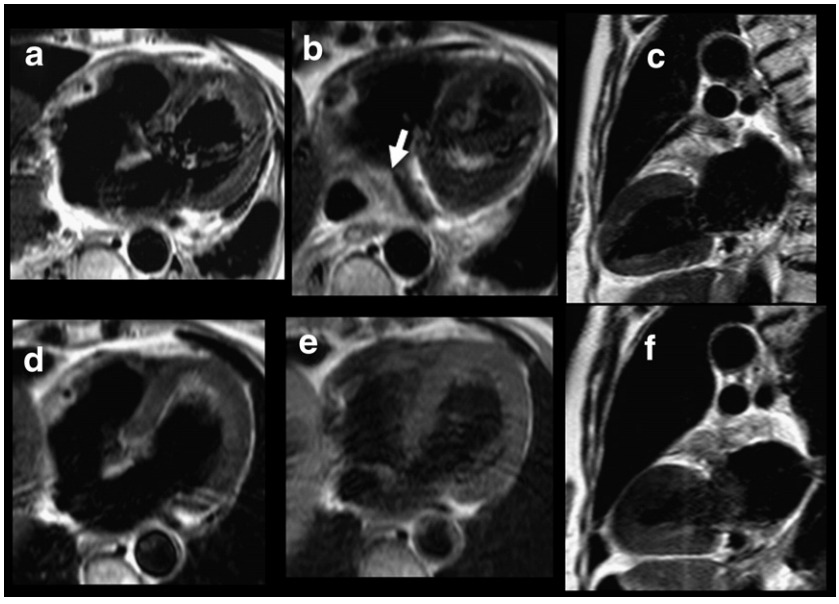

Fig. 4. T2-weighted magnetic resonance images 4 days (a–c) and 8 days (d–f) after the initiation of R-CHOP therapy. Marked regression of the tumor was observed 4 days after the treatment (arrow) and complete disappearance of the tumor was observed 8 days after the treatment.

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International Journal of Cardiology 109 (2006) 125 – 126

International Journal of Cardiology

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Letter to the Editor

MDCT of the anomalous origin of the right coronary artery from the left sinus of Valsalva as a single coronary artery

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Received 22 March 2005; accepted 26 March 2005
Available online 16 May 2005

Keywords: Coronary artery anomaly; MDCT; Virtual angioscopy

1. Case report

A 31-year-old man underwent multi-detector-row computed tomography (MDCT) coronary angiography because of episodes of chest pain followed by syncope in the early morning. He was referred from another hospital where his Holter ECG had shown transient ST-segment elevation on inferior extremity leads and sinus bradycardia. Conventional coronary angiography was performed but the right coronary artery (RCA) could not be visualized. Myocardial perfusion scintigraphy showed no perfusion defect after exercise. MDCT was performed using an Aquillion 16 (16-detector-row, Toshiba Medical, Tokyo, Japan). The scan protocol and image reconstruction method have been reported previously [1]. The reconstructed data were transferred to a computer workstation (M 900 quadra, AMIN, Tokyo, Japan) for processing the surface volume rendering and virtual angioscopic images. The volume rendering image (Fig. 1a) showed that the RCA arose from the left sinus of Valsalva and coursed anteriorly between the aortic root and the pulmonary artery. The axial image (Fig. 1b) showed an acute angled take-off of the RCA from the left main coronary artery. A 3D virtual angioscopic image (Fig. 2) also demonstrated that the RCA originated from the proximal portion of the left main coronary artery. With hesitation about surgical treatment, the patient was maintained on oral medication by isosorbide dinitrate uneventfully.

2. Discussion

The anomalous origin of the RCA is a rare condition, but has clinical importance because nonfatal or fatal

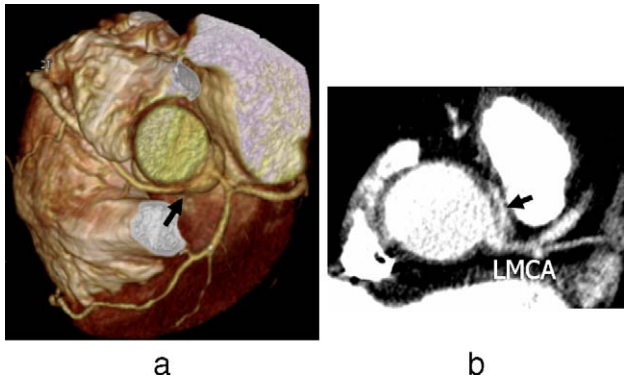

Fig. 1. (a) Volume rendering image showing the anomalous origin of the right coronary artery (arrow) which arises from the left sinus of Valsalva and courses between the ascending aorta and the pulmonary artery. Intramural course of the proximal portion of the right coronary artery within the aortic wall can not be observed on this image. (b) Axial image shows the right coronary artery (arrow) arising from the proximal portion of the left main coronary artery (LMCA).

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0167-5273/$ - see front matter
doi:10.1016/j.ijcard.2005.03.077

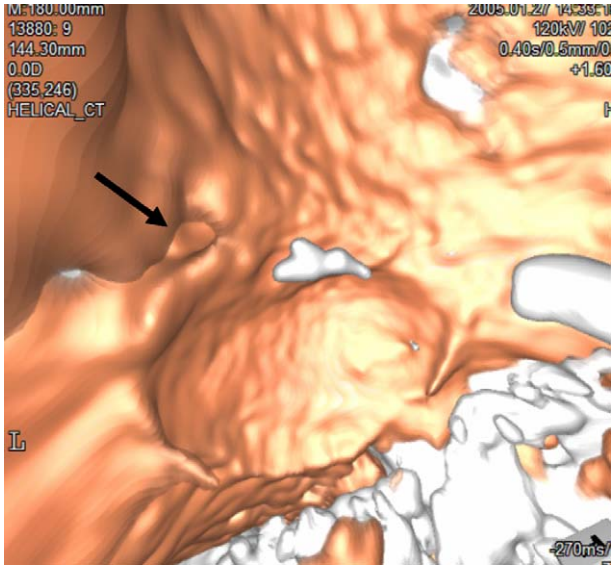

Fig. 2. Three-dimensional virtual angioscopic image showing a small orifice of the right coronary artery (arrow) arising from the left main coronary artery.

myocardial infarction and sudden death occur in up to 30% of patients [2–4]. In the majority of patients, the RCA arises from the left sinus of Valsalva, separately from the left main coronary artery. On the other hand, the anomalous origin of the RCA from the left main coronary artery as a single coronary artery is extremely rare [5]. The causes of myocardial ischemia in this anomaly remain unclear, but the acute angle take-off and kinking of the RCA as it arises from the left main coronary artery, flap-like closure of the abnormal coronary orifice, compression of the RCA when it courses within the aortic wall or between the aorta and the pulmonary artery, and spasm of the anomalous RCA have been thought to be the possible mechanisms [6]. In our patient, MDCT demonstrated acute angle take-off of the RCA from the left main coronary artery and intramural course within the aortic wall. Although these findings suggest possible causes of myocardial ischemia, our data could not clarify the exact mechanism of myocardial ischemia because MDCT images were obtained only in end-diastole, but not in systole during which ostial stenosis or compression of the RCA within the aortic wall might have occurred. In addition, the flap-like texture of the RCA orifice might have been overlooked because spatial resolution of MDCT was limited. The future development in the MDCT hardware which will provide higher spatial resolution and allow motion analysis during the whole cardiac cycle would be more informative for the evaluation of the mechanisms by which myocardial ischemia is provoked in patients with the anomalous origin of the RCA.

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Circ J 2005; **69:** 1047–1051

Efficacy of Multislice Computed Tomography for the Detection of Acute Coronary Syndrome in the Emergency Department

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Background The diagnosis of acute coronary syndrome (ACS), especially non-ST-elevation myocardial infarction and unstable angina in the emergency department (ED) still remains a challenge. Multislice computed tomography (MSCT) allows assessment of not only coronary artery stenoses and occlusions, but also assessment of coronary artery plaques and myocardial perfusion status.

Methods and Results MSCT was performed in 31 patients who were admitted to the ED because of chest pain persisting at least 30 min and non-diagnostic ECG changes and normal serum enzyme concentrations. Using MSCT, ACS was defined by coronary artery stenosis ≥75% accompanied by computed tomography (CT)-low-density plaques, and/or by the presence of myocardial perfusion defects. ACS was confirmed by coronary stenosis ≥75% by coronary angiography and/or subsequent elevation of troponin I concentration. In total, 22 patients were diagnosed as having ACS. MSCT detected stenoses with CT-low-density plaques in 21 and non-transmural myocardial perfusion defect in 3 patients. There was 1 false-positive and 1 false-negative result. The sensitivity and specificity of MSCT to identify ACS was 95.5% and 88.9%, respectively.

Conclusion MSCT provides diagnostic operating characteristics suitable for triage of patients with ACS in the ED. (*Circ J* 2005; **69:** 1047–1051)

Key Words: Acute coronary syndrome; Emergency department; Multislice computed tomography

The management of patients with suspected acute coronary syndrome (ACS) in the emergency department (ED) still remains a challenge, even with current diagnostic modalities, because ACS constitutes a broad classification of clinical status that includes ST-elevation myocardial infarction (MI), non-ST elevation MI (NSTEMI) and unstable angina (UA)[1] In a relatively small population of patients with ACS the diagnosis and therapeutic strategy are clearly established on the basis of the ECG and initial cardiac enzyme concentrations. However, although cardiac enzymes are sensitive markers of MI[2] by definition, they are not sensitive to UA[3] and furthermore, diagnosing ACS by cardiac enzymes may require 4–12 h to have elapsed after the onset of ACS. Echocardiography and myocardial perfusion single-photon emission computed tomography (SPECT) have incremental diagnostic value, but they are still insensitive for the diagnosis of UA[4,5]

The recent introduction of multislice computed tomography (MSCT) with its high spatial resolution has allowed direct visualization of the coronary arteries. MSCT is capable of not only detecting significant coronary artery stenoses and occlusions[6,7] but also evaluating the texture of coronary artery plaques[8–10] and myocardial perfusion defects[11] Because ACS is a consequence of rupture of lipid-rich plaques and subsequent thrombus formation[12,13] detecting rupture-prone, vulnerable plaques would be the most reliable diagnostic procedure in patients with suspected ACS. In addition, the presence of myocardial perfusion defects on contrast-enhanced myocardial images should confirm the diagnosis of ACS. We, therefore prospectively evaluated the diagnostic accuracy of MSCT in patients with suspected ACS, using a combined assessment of coronary artery stenosis, plaque texture and the myocardial perfusion status.

(Received April 18, 2005; revised manuscript received May 30, 2005; accepted June 29, 2005)

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Methods

Patients

After obtaining informed consent, we prospectively studied 34 patients who presented to the ED between July 2002 and December 2004 with chest pain. MSCT scans were performed as early as possible after resolution of chest pain. Inclusion criteria were (1) >30 min of chest pain compatible with myocardial ischemia within 6 h of presentation, (2) normal or non-diagnostic ECG changes, and (3) normal initial concentrations of serum troponin-I (≤0.1 ng/ml), creatine kinase (CK, ≤253 mIU/ml for men and ≤182 mIU/ml for women) and CK-MB (≤25 mIU/ml). The Thrombolysis in Myocardial Infarction (TIMI) risk score was calculated on the basis of age, risk factors, coro-

Table 1 Patient Characteristics

	ACS (n=22)			Non-ACS (n=9)
	NSTEMI (n=14)	UA (n=8)	Total (n=22)	
Age (years)	60±13	57±16	58±14	50±13
Men (%)	13 (93%)	8 (100%)	21 (95%)	8 (89%)
TIMI risk score	1.5±0.5	1.3±0.5	1.4±0.5	1.1±0.3

ACS, acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; TIMI, Thrombolysis in Myocardial Infarction.

Table 2 Scan Parameters

	4-slice CT (n=26)	16-slice CT (n=6)
Heart rate (beats/min)		
Beginning	51±5	55±8
End	55±7	59±4
Contrast transit time (s)	21±3	19±4
z-axis coverage (mm)	105±4	112±9
Breath hold time (s)	35±2	34±5

CT, computed tomography.

nary stenosis in the prior angiographic study, the presence of ST elevation, anginal symptoms, use of nitrites and elevated serum cardiac enzymes[14]

Medical exclusion criteria included ST-elevation MI, pregnancy, previous history of MI and severe congestive heart failure (unable to lie flat). MSCT exclusions included previous history of allergy to iodine, cardiac arrhythmias (atrial fibrillation, frequent supraventricular or ventricular premature contractions), renal dysfunction (serum creatinine >1.5 mg/dl) and severe left ventricular dysfunction assessed by echocardiography (left ventricular ejection fraction <30%), and severe coronary artery calcification, which was defined by the presence of computed tomography (CT)-high-density mass (<250 Hounsfield units (HU)) occupying more than 50% of the vessel area. Conventional coronary angiography was performed within 24 h of the onset of chest pain in all patients using Judkin's technique.

Definition of ACS

Because the enrolled patients did not fulfil the definition of ACS established by the American College of Cardiology and the American Heart Association (ACC/AHA)[1] which is based on ECG and enzymatic criteria, NSTEMI was retrospectively defined as a subsequent increase in troponin-I (>0.1 ng/ml) with a temporal pattern consistent with acute MI and/or a ≥75% epicardial coronary artery stenosis on subsequent coronary angiograms. Confirmation of UA required ≥75% coronary artery stenosis or positive abnormal stress ECG-gated SPECT using a rest ^{201}thallium/stress ^{99m}Tc-tetrofosmin dual-isotope separate acquisition protocol[15,16] performed during hospitalization or in the subsequent 2- to 4-week follow-up period.

MSCT

MSCT was performed prior to angiography in all patients using either a SOMATOM Volume Zoom (4-detector-row, Siemens, Germany) with a collimation 1.0 mm, table feed 1.5 mm/rotation, 140 kV, 320 mA and gantry rotation time 500 ms or an Aquillion 16 (Toshiba Medical, Tokyo, Japan) with a collimation 0.5 mm, table feed 3.2–4.2 mm/rotation, 140 kV, 102 mA and gantry rotation time 400 ms. The scan protocol and image reconstruction method have been reported previously[17] Briefly, metoprolol (20–80 mg) was given 60 min prior to the scan in order to reduce the heart rate to enable performance of the single-phase algorithm[9] Nitroglycerin (Myocol Spray 0.3 mg, Toa Eiyo, Tokyo, Japan) was also administered sublingually 5 min prior to the scan. Following determination of contrast transit time from the cubital vein to the ascending aorta by injecting 15 ml of nonionic contrast medium (Iomeron 300 or 350 100 ml syringe, Eisai, Tokyo, Japan), the remaining contrast medium (85 ml) was injected at 2.6–2.8 ml/s. Image reconstruction was made with a reconstruction window (250 ms for a 4-detector-row equipment and 200 ms for a 16-detector-row equipment) positioned immediately before the atrial contraction period, which could be recognized by the peak of the P wave on the monitor ECG. The reconstructed data were transferred to a computer workstation (3D Virtuoso, Siemens, Germany for the SOMATOM Volume Zoom and M 900 quadra, AMIN, Tokyo, Japan for the Aquillion 16) for post-processing the volume rendering, curved and cross-sectional multiplanar reformation images. The presence of coronary artery plaques was carefully inspected on the axial and multiplanar reformation images. Plaques containing CT density <50 HU were considered as soft plaques[8,9] In patients with multiple coronary artery plaques, CT density measurements were performed on the plaque at the lesion of maximum stenosis. Myocardial perfusion defect was defined as an area that did not enhance as brightly as the surrounding myocardium on at least 5 consecutive multiplanar or axial images at 1 mm intervals. To accept a perfusion defect as a definite abnormality, there had to be coronary artery stenoses or plaques in a matching location. Definition of ACS by MSCT included the presence of coronary stenosis ≥75% on curved multiplanar reformation images with soft plaques and/or the presence of a myocardial perfusion defect. The radiation dose for our MSCT protocol was estimated to be 4–5 mSv for 4-detector-row and 7–8 mSv for 16-detector-row equipment.

Statistics

All the data are presented as mean±standard deviation. Sensitivity and specificity of MSCT to detect ACS were calculated in the standard fashion. Cohen's κ was used to assess interobserver variations in the MSCT determination of coronary stenosis.

Results

MSCT scans with sufficient image quality for evaluation of stenoses and plaques were obtained in 31 patients; 3 patients were excluded from the study because they had severe coronary artery calcification that hampered the assessment of stenosis. Thus, the study group comprised these 31 patients (Table 1). All patients had a TIMI risk score ≤2. Fourteen patients had a subsequent elevation of troponin I concentration. Significant coronary artery stenosis was detected in 21 patients. Using an enzymatic and angiographic definition, NSTEMI was diagnosed in 14 patients; 8 patients were diagnosed as having UA on coronary angiography (n=7) and positive exercise myocardial perfusion SPECT during a 6-week follow-up period (n=1); 9 patients did not show significant coronary stenoses or occlusions on angiography and their serial serum troponin concentrations and exercise myocardial perfusion SPECT were normal.

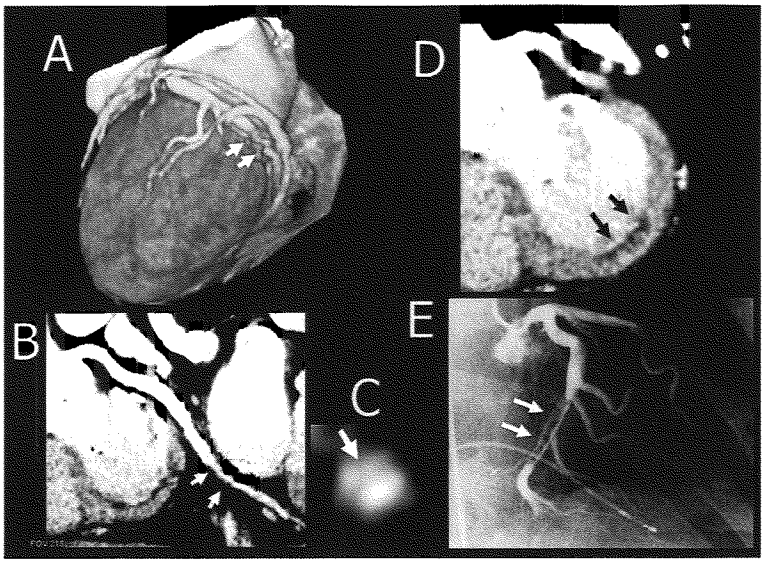

Fig 1. A 48-year-old man with non-ST-segment elevation myocardial infarction. Volume rendering (A) and curved multiplanar reformation (B) images show stenosis in the distal portion of the left circumflex artery (arrows). An axial image (C) shows stenosis with a CT-low-density plaque (42 HU, arrow). A short-axis image of the left ventricle (D) shows a thin-layered subendomyocardial contrast defect in the infero-lateral left ventricular wall (arrows). Coronary angiography (E) shows patent left circumflex artery but a large thrombus (arrows).

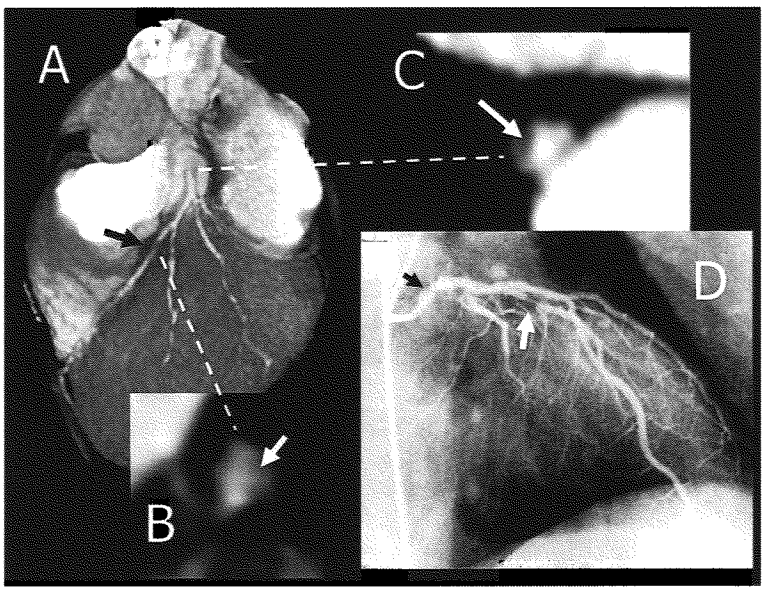

Fig 2. A 33-year-old man with unstable angina. Volume rendering image (A) shows stenosis in the left anterior descending artery (arrow) and a cross-sectional multiplanar reformation (MPR) image (B) shows high-grade stenosis with a CT-low-density plaque (44 HU, arrow). Cross-sectional MPR image of the left main coronary artery (C) also exhibits mild stenosis with a CT-low-density plaque (14 HU, arrow). Coronary angiography demonstrates high-grade stenosis in the left descending artery (white arrow) and mild stenosis in the left main coronary artery (black arrow).

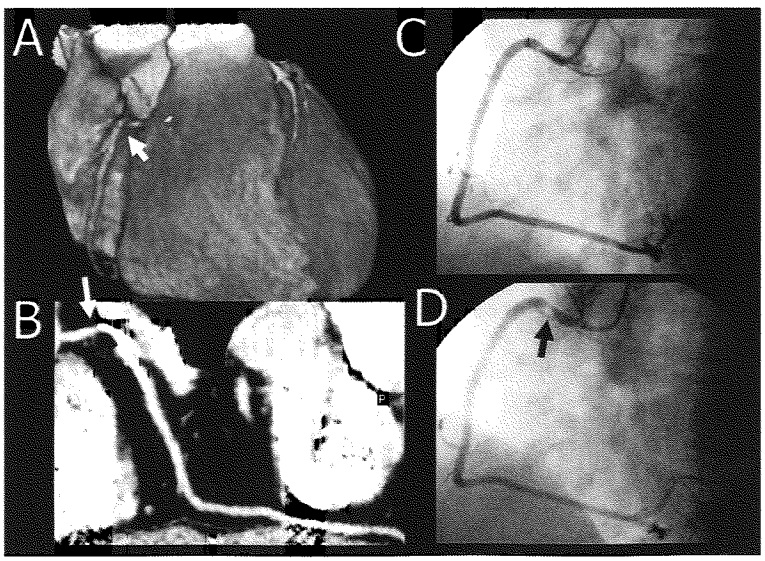

Fig 3. False-positive MSCT result in a patient with vasospastic angina. Volume rendering (A) and curved multiplanar reformation (B) images show stenosis in the proximal portion of the right coronary artery (arrows). Coronary angiography shows no stenosis (C), but spasm was provoked after acetylcholine injection (D, arrow).

MSCT was performed in all patients without complications related to β-blocker or contrast medium. The scaning parameters are listed in Table 2. MSCT scans were completed within 15 min and image processing required 10–20 min depending on the complexity of the coronary artery status. The whole MSCT procedure from administration of β-blocker to completion of image analysis required less than 120 min in all patients. Cohen's κ was 0.92, indicating a good interobserver agreement in the coronary artery stenosis measurements by MSCT. MSCT detected significant coronary artery stenosis in 13 patients with NSTEMI and in these patients, the stenosis was unexceptionally accompanied by soft plaques. The CT density of the plaque was 23.5±22.4 HU (−32 to 48 HU). In 3 of the patients with NSTEMI, there was a thin-layered subendocardial contrast defect in the myocardial territory supplied by the culprit coronary artery (Fig 1). In the 8 patients diagnosed with UA, MSCT detected significant coronary artery stenosis associated with soft plaques (CT density 38.4±6.9 HU (28–47 HU)). Thus, MSCT detected ACS in 21 patients (sensitivity 95.5%). The MSCT and angiographic images in a patient with NSTEMI are shown in Fig 2. On the other hand, MSCT gave negative results for 8 of the 9 patients without ACS (specificity 88.9%). In these 9 patients, the follow-up myocardial perfusion SPECT was normal, and they had no ischemic episodes in the follow-up period of 4 weeks. In 1 patient in whom MSCT gave a false-positive result (initial coronary angiography was normal), the repeat coronary angiography performed 2 weeks after admission documented spasm in the proximal portion of the right coronary artery after provocation by intracoronary injection of acetylcholine (Fig 3).

Discussion

The present study shows the feasibility of MSCT in the ED for detecting patients with ACS who did not manifest ECG and enzymatic evidence. The goal of non-invasive imaging in the era of sensitive serum enzymes needs additive clinical value over infarct detection. Cardiac enzymes only detect the presence of myocardial necrosis, which represents only a fraction of ACS, and they are insensitive to UA. Although echocardiography can detect the regional wall motion abnormality that may persist for hours after transient ischemia, a phenomenon that is known as myocardial stunning, its sensitivity to detect ACS is limited, especially when the chest pain resolves![18] Myocardial perfusion SPECT is the most developed imaging modality for patient triage in the ED[19,20] and although its sensitivity is excellent for the detection of infarction, particularly with the ^{99m}Tc tracers, it is insensitive for detection of UA. For example, in a cohort of more than 1,000 patients with acute chest pain, normal images were acquired in 7 of 32 patients with ACS (22%)[21] and in a multicenter trial of 102 patients with typical chest pain, but non-diagnostic ECG, only 3 of 15 patients with UA had abnormal myocardial perfusion SPECT?[22] More recently, Abbott et al reported that 144 of 2,601 patients with acute chest pain (6%) had false-negative results based on serum enzymes and rest myocardial perfusion SPECT using ^{99m}Tc-sestamibi?[23] Because rupture of vulnerable plaque and the subsequent thrombosis is the cause of ACS![12,13] direct visualization of ruptured plaques and coronary artery obstruction or narrowing is the ultimate goal of using a diagnostic imaging modality for patients suspected of having ACS. Although the spatial resolution of currently available MSCT equipment is unsatisfactory for distinguishing ruptured plaques from non-ruptured plaques, MSCT can accurately detect coronary artery stenoses and occlusion[6,7] as well as plaque texture, by measuring the CT density of the plaque[8,9] In a previous study from our laboratory![10] the plaque CT density in the infarct-related coronary artery in patients with ACS was exceptionally lower than 48 HU (−12 to 48 HU), whereas it was higher than 46 HU (46–101 HU) in patients with stable angina. Komatsu et al also demonstrated that plaque with a CT density less than 50 HU corresponded to angioscopically detected yellow plaque, another marker of vulnerable plaques, with a sensitivity of 80% and specificity of 87% in infarct-related arteries?[24] These studies suggest that in the majority of patients with ACS the plaques in the infarct-related artery can be identified by measuring the CT density. Myocardial perfusion defect, as documented by the presence of non-contrast enhanced ventricular myocardium, is also evidence of infarction![11] With its high spatial resolution, MSCT may be more sensitive than myocardial perfusion SPECT for detecting subendocardial myocardial ischemia. However, in the present study population only 3 of 14 (21%) patients with NSTEMI exhibited a contrast defect in the subendomyocardium. This insensitivity can be explained by our patient selection based on the absence of increased cardiac enzyme concentrations.

Study Implications

The revised ACC/AHA guidelines for the management of patients with UA and NSTEMI has encouraged rapid decision-making by the physician in the diagnosis of UA and NSTEMI, using evidence-based standards for risk stratification, prognostic use of biologic markers, and proper use of antiplatelet and antithrombotic therapy! Missing the diagnosis of ACS doubles the risk-adjusted mortality?[2] Despite an initial risk assessment using ECG and cardiac enzymes, approximately 2% of patients with ACS are inappropriately discharged home from the ED?[25] On the other hand, aggressive, invasive procedures are not fully justified because they may expose patients with a low likelihood of ACS to angiography-related complications and excessive medical expense. Our study, which targeted patients with a low likelihood of ACS, suggests that MSCT can be the first-choice imaging modality because of its noninvasiveness and low medical expense.

Study Limitations

The foremost limitation is the small patient population enrolled. Moreover, our diagnostic criteria for ACS was based on indirect evidence including enzyme elevation, angiographic coronary stenosis and positive exercise myocardial perfusion SPECT test result. Intravascular ultrasound or coronary angioscopy should have been performed to confirm ruptured plaque and subsequent thrombus formation.

The present study utilized 2 different types of MSCT equipment with different slice thicknesses to define soft plaques. The definition of soft plaques (<50 HU) has been established with 4-slice and 8-slice CT equipment[8,24] Although a direct comparison between plaque CT densities derived from a 4-slice scanner and those from a 16-slice scanner in the same individuals has not been made previously, it is plausible that the thinner the slice thickness the lower the plaque CT density (far less than 50 HU) that would be obtained because the thinner slice would have

less partial volume effect because of the contrast-enhanced, adjacent tissue. A revised definition of soft plaques for 16-slice and 64-slice equipment is warranted.

The temporal resolution of MSCT is limited and the majority of patients require administration of β-blockers prior to the scan in, which may cause vasospasm and lead to a false-positive MSCT results, as occurred in one of the present patients.

As mentioned previously, direct visualization of coronary artery plaque rupture and subsequent thrombosis would be the most reliable method of establishing the diagnosis of ACS. Future improvements in the spatial resolution of MSCT by increasing the number of detectors or by introducing flat panel detectors will enable assessment of these morphological alterations.

These limitations aside, our study indicates that MSCT provides diagnostic operating characteristics suitable for triage of patients with ACS in the ED.

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