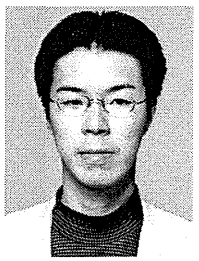

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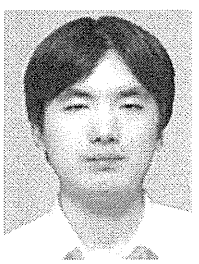

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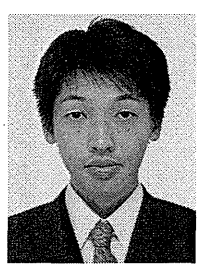

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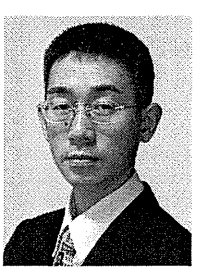

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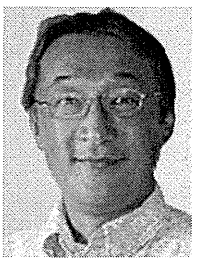

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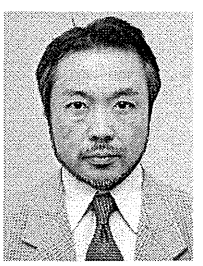

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Original Article

Cardio-Ankle Vascular Index in Heterozygous Familial Hypercholesterolemia

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Aim: **The cardio-ankle vascular index (CAVI) is a new non-invasive marker of arterial stiffness and atherosclerosis. The purpose of this study was to compare CAVI in patients with heterozygous familial hypercholesterolemia (FH) and in healthy controls.**
Methods: **82 FH subjects (27 males, 65 females), aged 53.7 ± 13.6 years without clinical symptoms of cardiovascular diseases and 359 healthy controls (121 males, 238 females), aged 43.9 ± 14.9 years, were examined. CAVI was measured using the system VaSera® 1500.**
Results: **CAVI in FH patients was significantly higher (8.0 ± 1.4) than in healthy subjects (7.5 ± 1.3) $p=0.002$; however, age, sex and BMI adjusted CAVI did not differ significantly ($p=0.061$) between the FH group (7.5, CI: 7.3; 7.7) and control group (7.7, CI: 7.6; 7.7).**
Conclusion: **The study showed no significant difference in CAVI between heterozygous FH and healthy controls.**

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Key words; Atherosclerosis, Cardio-ankle vascular index, Familial hypercholesterolemia, Statins, Ezetimibe

Introduction

Major causes of death in developed countries are cardiovascular and cerebrovascular diseases, which arise from the progress of atherosclerosis in certain arteries. Atherosclerosis is a chronic disease that develops over many years and usually does not cause symptoms, until its severity narrows the artery, or until it causes a sudden obstruction. A very important aspect of atherosclerosis is that its progression may be stopped or even reversed by clinical intervention. For example, aggressive lowering of elevated cholesterol levels leads to a reduction in both the physical extent of atherosclerosis and the incidence of coronary artery disease (CAD) and stroke[1-3]; therefore, it is very important to detect atherosclerotic changes early in order to prevent future clinical cardiovascular events more effectively. For this purpose, a simple, quantitative and non-invasive assessment of early stages of atherosclerosis is required. Several methods for the evaluation of

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Table 1. Diagnostic criteria for familial hypercholesterolemia[27]

Age	Total cholesterol (LDL-cholesterol) cut-off points (mmol/L)			
Age (years)	First-degree relative with FH	Second-degree relative with FH	Third-degree relative with FH	General population
<20	5,7 (4,0)	5,9 (4,3)	6,2 (4,4)	7,0 (5,2)
20-29	6,2 (4,4)	6,5 (4,7)	6,7 (4,8)	7,5 (5,7)
30-39	7,0 (4,9)	7,2 (5,2)	7,5 (5,4)	8,8 (6,2)
40+	7,5 (5,3)	7,8 (5,6)	8,0 (5,8)	9,3 (6,7)

A diagnosis of FH is made if cholesterol levels exceed the cut-off point. FH: familial hypercholesterolemia

arteriosclerosis have been introduced. Among them, high-resolution B-mode ultrasonography serves for the measurement of carotid intima-media thickness, a strong predictor of cardiovascular events[4-6]. Another widely used non-invasive method for the detection of atherosclerosis is the measurement of large artery stiffness. A very useful method for arterial stiffness evaluation is arterial pulse-wave velocity (PWV) measurement[7, 8]. PWV enables to detect arteriosclerosis in any part of the body and brachial-ankle PWV has been widely used to detect early stages of arteriosclerosis[9-11]. Brachial-ankle PWV has been shown to be a predictor of coronary artery disease and serves for the prognosis of acute coronary syndrome[10, 12]; however, there are several problems with its use in clinical practice. PWV measurement is rather technically difficult, its reproducibility is low and it is age-dependent and blood pressure-dependent; thus, the results are affected also by changes in BP during measurement[13, 14], which is why another simple quantitative index for the early diagnosis of atherosclerosis was required. Recently, a new method for the atherosclerosis index (cardio-ankle vascular index - CAVI) was introduced[14]. CAVI is adjusted for blood pressure based on stiffness parameter beta. The measurement of CAVI is not affected by changes in blood pressure during measurement[15], so CAVI is a pressure-independent index indicating the natural stiffness of the blood vessels, based on the stiffness parameter β[14, 16]. It is a marker suitable for atherosclerosis estimation in various arteries, including the femoral artery, aorta and tibial artery[17]. Several studies have shown the usefulness of CAVI for the detection of atherosclerosis[18-22]. The results of CAVI measurement have been reported in patients with various cardiovascular risk factors, such as obesity and metabolic syndrome[23], essential hypertension[20], diabetes mellitus[24, 25], and smoking[26]; however, no study has yet investigated CAVI in patients with inherent hyperlipoproteinemia, primarily in familial hypercholesterolemia (FH).

Aim

The aim of this study was to determine whether CAVI differs in patients with heterozygous FH as compared to healthy controls.

Methods

Patient Groups

The studied population consisted of 82 subjects with FH aged 18 and above from the Outpatients Department for lipid disorders, who underwent regular control examination between January 2010 and November 2010. Diagnostic criteria for FH were consistent with international criteria and were based on those of the US MEDPED program and publication of Williams *et al.*[27, 28]: FH was diagnosed when the cut-off values for total cholesterol as well as LDL-cholesterol exceeded the values given in **Table 1**. All FH patients were examined by molecular-biologic methods: firstly, gene for apolipoprotein B (p.Arg3500Gln mutation) was analyzed, and then analysis of the gene for LDL-receptor was performed in those patients, who had no mutation of the gene for apolipoprotein B. Mutation p.Arg3500Gln in the gene for apolipoprotein B was found in 20 patients (24,1%), and mutation in the gene for LDL-receptor in 36 patients (43%). Detailed information on the methods and procedures used for analysis of the LDL-receptor gene and the gene for apolipoprotein B were published recently[29, 30]. In all patients, the causes of secondary hypercholesterolemia (e.g. hypothyroidism, renal disease, and liver disease) were excluded.

All patients with heterozygous FH without arteriosclerotic signs (no clinical symptoms and no cardiovascular diseases in history) were included in this study. All patients with previous stroke or transient ischemic attack, previous angina pectoris or myocardial infarction, documented chronic ischemic heart disease, peripheral artery disease, cardiomyopathy or sig-

nificant valvular disease, arrhythmia and also patients with renal or heart failure were excluded from the study. All FH patients were treated with hypolipidemic drugs (statins or combination statin + ezetimibe).

The control group consisted of 359 healthy subjects aged from 20 to 79 years. All subjects included in the control group were examined by a general practitioner and sent for CAVI examination if they fulfilled the following criteria: blood pressure <140/90 torr; glycemia <6.0 mmol/L; total cholesterol <5.0 mmol/L; personal history without cardiovascular diseases, hypertension, hyperlipidemia, diabetes mellitus, renal diseases and gout. All subjects in the control group had physiological ECG. All subjects in this study (FH group as well as control group) were Caucasian and of Slavic origin.

The study was approved by the ethics committee of St. Anne's Faculty Hospital Brno and written informed consent was obtained from the participants in the study at the beginning of the study. Informed consent was also obtained from all FH patients for genetic analysis.

Anthropometric Indices

Height and weight were measured by trained staff; BMI was calculated as weight (kg)/height squared (m^2).

Biomedical Markers

Blood pressure was measured twice (in a sitting position): once in the waiting room upon arrival and again after at least 10 minutes of rest, and the mean was calculated. Blood samples were taken in the morning after 8-10 hours of fasting, 1-2 weeks before CAVI measurement; they were sent to the laboratory for analysis within half an hour after collection. All laboratory tests were carried out in the same laboratory. Serum lipid and lipoprotein analyses were performed on an ADVIA 1650 analyzer (Siemens, Germany) with commercially available kits: total cholesterol and triglycerides were assayed by the enzymatic colorimetric method (Roche Diagnostic GmBH), HDL-cholesterol was assessed by the homogenous method for direct measurement without precipitation (Sekisui Medical, Tokyo), and LDL-cholesterol was calculated according to the Friedewald equation[31].

CAVI Measurement

CAVI was measured using the system VaSera® 1500 (Fukuda Denshi Co., Tokyo, Japan), adopting the oscillometric method for blood pressure measurement. It does not simultaneously measure blood pressure in 4 limbs but first measures at the right brachial and ankle and then at the left brachial and ankle. Thus, arteries on the right and left sides are alternately pressurized with the other side open. This procedure does not only reduce the burden on examinees but also enables more accurate measurement. The CAVI calculation is based on stiffness parameter β obtained by means of the Bramwell-Hill equation[14, 32]:

$CAVI = (\ln Ps/Pd) \times 2\rho/\Delta P \times PWV^2$, where Ps and Pd are systolic and diastolic blood pressures, respectively; PWV is the pulse wave velocity between the heart and ankle; ρ is blood density; and ΔP is pulse pressure.

The CAVI was measured by trained staff, with the participant resting in a supine position and the head held in a midline position. ECG and phonocardiography were monitored during the measurement. In order to limit the influence of diurnal variations, all subjects were always examined at the same time, 8:00-11:00 AM. The examination was conducted in a quiet room and at a stable temperature of 21-22℃.

Statistics

The characteristics of the subjects were described by the proportions for categorical variables and the mean (and SD) of continuous variables. Between-group comparisons of proportions and means were conducted by Fisher's exact test and the unpaired *t*-test. Spearman's rank correlation was computed to assess the relationship between CAVI and age or BMI. Analysis of covariance was used to adjust for age, sex, and BMI in the comparisons of CAVI and blood pressure. Statistical analyses were performed using SPSS 19.0.1 (IBM Corporation, 2010).

Results

Basic characteristics of the study populations and non-adjusted blood pressure and CAVI values are shown in **Table 2**. FH patients were older than healthy controls ($p<0.001$). FH patients have significantly higher systolic blood pressure, ($p=0.012$), diastolic blood pressure ($p=0.031$) and BMI ($p=0.016$). No statistically significant difference in the proportion of men/women was found ($p=1.000$). CAVI was significantly higher in the FH group than in the control group ($p=0,002$).

All FH patients were treated with hypolipidemic drugs - statins or combination statin with ezetimibe; the period from treatment onset to the CAVI measurement was 9.2 ± 4.2 years (mean ± SD). The generic names of the statins, mean dose and number of patients treated with particular drugs are shown in **Table 3**, plasma lipids in patients before treatment with

Table 2. Baseline characteristics of patients with heterozygous familial hypercholesterolemia and control group

	Familial hypercholesterolemia ($N=82$)	Control group ($N=359$)	p^*
Male †	27 (32.9%)	121 (33.7%)	1.000
Age § (years)	53.7 ± 13.6	43.9 ± 14.9	<0.001
BMI § (kg/m^2)	26.0 ± 3.9	24.8 ± 4.2	0.016
Systolic BP § (mmHg)	132.0 ± 12.8	127.3 ± 15.8	0.012
Diastolic BP § (mmHg)	80.4 ± 8.6	77.9 ± 9.7	0.031
CAVI §	8.0 ± 1.4	7.5 ± 1.3	0.002

CAVI: cardio-ankle vascular index; BP: blood pressure; BMI: body mass index
†Number and percentage of categorical variables; §mean ± SD of continuous variables;
*Fisher's exact test was used for testing the statistical significance of differences in categories, *T*-test was used to test the statistical significance of differences in the distribution of continuous variables.

Table 3. Summary of the treatment of patients with familial hypercholesterolemia (generic name of the statins, their dose, combination with ezetimibe)

	Number of patients treated by statin monotherapy	Dose of statins (mg)	Number of patients treated by combination of statin with ezetimibe 10 mg N (%)
Simvastatin	10	36.4 ± 16.7	8 (80)
Fluvastatin	3	80.0 ± 0.0	2 (67)
Atorvastatin	45	40.9 ± 20.2	27 (60)
Rosuvastatin	24	33.3 ± 9.43	5 (21)
Total	82	40.9 ± 20.1	42 (51)

The dose of statins is given as the mean ± SD

Table 4. Blood lipids in patients with FH before therapy and during therapy with statins at the time of CAVI examination

	Baseline (without statin treatment)	At the time of CAVI measurement (with statin treatment)	P
Total cholesterol (mmol/L)	9.55 ± 1.86	6.22 ± 1.51	<0.001
LDL-cholesterol (mmol/L)	7.13 ± 1.78	4.05 ± 1.33	<0.001
HDL-cholesterol (mmol/L)	1.65 ± 0.45	1.60 ± 0.42	0.366
Triglycerides (mmol/L)	1.69 ± 0.95	1.29 ± 0.80	<0.001

Results are expressed as the mean ± SD; p-paired *t*-test on log-transformed data

statins and at the time of CAVI measurement are shown in **Table 4**. A positive correlation was found between the duration of treatment with statins/ezetimibe and CAVI value (r_s=0,344, p=0,004) (**Fig. 1**).

CAVI and blood pressure were adjusted for age, BMI and sex due to the statistically significant correlation of both CAVI and blood pressure with these descriptive factors. Adjusted values are shown in **Table 5**. Age-, sex- and BMI-adjusted CAVI became slightly, insignificantly (p=0,061) lower in FH patients than in the control group; adjusted systolic and diastolic blood pressure did not differ between the two groups.

We found a positive significant correlation between CAVI and age in both groups ($p<0.001$), and between CAVI and BMI in the control group ($p<0.001$) (**Fig. 2**).

Discussion

The aim of the present study was to compare CAVI in healthy subjects and in patients with heterozygous FH, who are at high risk of premature atherosclerosis and consequently of coronary heart disease.

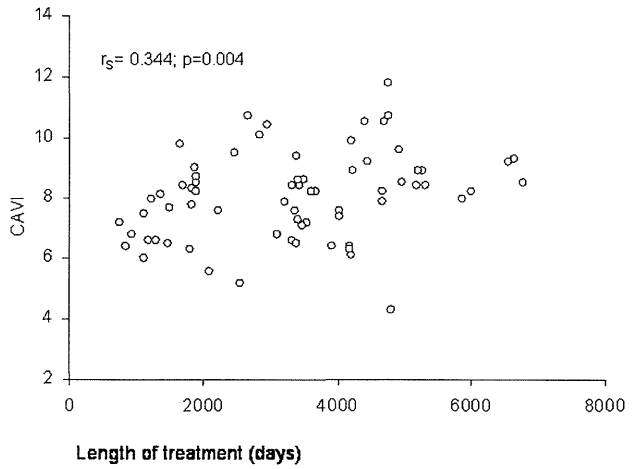

Fig. 1. Spearman's correlation of CAVI with length of treatment with statin/ezetimibe in heterozygous familial hypercholesterolemia group

CAVI: cardio-ankle vascular index; r_s: Spearman's rank correlation coefficient

No significant differences in CAVI were found in the group of 82 heterozygous FH patients treated with statins (or with combination statin and ezetimibe) when compared to healthy controls. FH is a genetic disorder presenting as premature atherosclerosis, primarily by coronary artery disease (CAD). It is an autosomal dominant disease caused by mutations in the LDL-receptor gene, or more rarely in the apolipoprotein B-100 gene[33, 34]. The phenotype of familial defective apolipoprotein B-100 is similar to that of patients with a mutation in the LDL-receptor gene and is not clinically distinguishable. Typical laboratory findings include very high levels of LDL-cholesterol (LDL-C); the main clinical symptom is premature atherosclerosis, primarily CAD[35]. Untreated FH heterozygotes may present with CAD at the age of 30-40 years and at the age of 50 years, 50% of men and 15% of women die of myocardial infarction[36]. The cumulative risk of fatal or non-fatal CAD is more than 50% at the age of 50 years in men and at least 30% in women aged 60 years[37, 38]. The progression of atherosclerosis and manifestation of cardiovascular disorders are therefore significantly accelerated in patients with FH in comparison to healthy population. The average age of HF patients in this study was 53.7 years; therefore, we expected CAVI, this very sensitive index of preclinical and clinical atherosclerosis, to be increased[20-22]; however, the values of CAVI did not significantly differ between the two studied groups after adjustment for age, BMI and gender. It has been demonstrated that high CAVI implies the progression of carotid and coronary arteriosclerosis[18, 19] and that CAVI might be more useful for the determination of coronary atherosclerosis probability than the assessment of carotid atherosclerosis by high-resolution B-mode ultrasonography[39]. We suppose that favourable CAVI values of FH patients in our study are the result of the highly restricted influence of cardiovascular risk factors. Atherosclerosis progress may be affected, except by age and gender, by other risk factors, such as increased BMI, hypertension, diabetes mellitus, increased LDL-cholesterol, low HDL-cholesterol or increased values of triglycerides. In our group with FH, values of blood pressure (after adjustment for age, gender and BMI) did not differ from the values in the control group and were within the physiological range. BMI was borderline (26 kg/m^2). Neither decreased HDL-cholesterol nor increased triglycerides were observed (**Table 4**) and diabetes mellitus was found only in two patients. The main risk factor was therefore represented by increased LDL-cholesterol; however, all patients with FH were treated long-term either with statins or with the combination of a statin and ezetimibe, which reduced plasmatic values of LDL-cholesterol by 45% (**Table 4**). Statins effectively reduce LDL-cholesterol plasma by the inhibition of HMG-CoA reductase, an enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis[40]. However, statins have also pleiotrophic, cholesterol-independent effects, such as increased nitric oxide bioactivity and the reduction of

Table 5. Adjusted means (95% confidence interval) of CAVI and blood pressure in patients with heterozygous familial hypercholesterolemia and control subjects

	Familial hypercholesterolemia (N=82)	Control group (N=359)	p^*
CAVI	7.5 (7.3; 7.7)	7.7 (7.6; 7.7)	0.061
Systolic BP (mm Hg)	129.1 (126.5; 131.7)	127.9 (126.6; 129.3)	0.479
Diastolic BP (mm Hg)	78.6 (76.8; 80.3)	78.3 (77.4; 79.1)	0.782

Adjusted for age, sex, and body mass index by analysis of covariance. *Standard t-test was used to analyze the statistical significance of differences in distribution of continuous variables; CAVI: cardio-ankle vascular index; BP: blood pressure

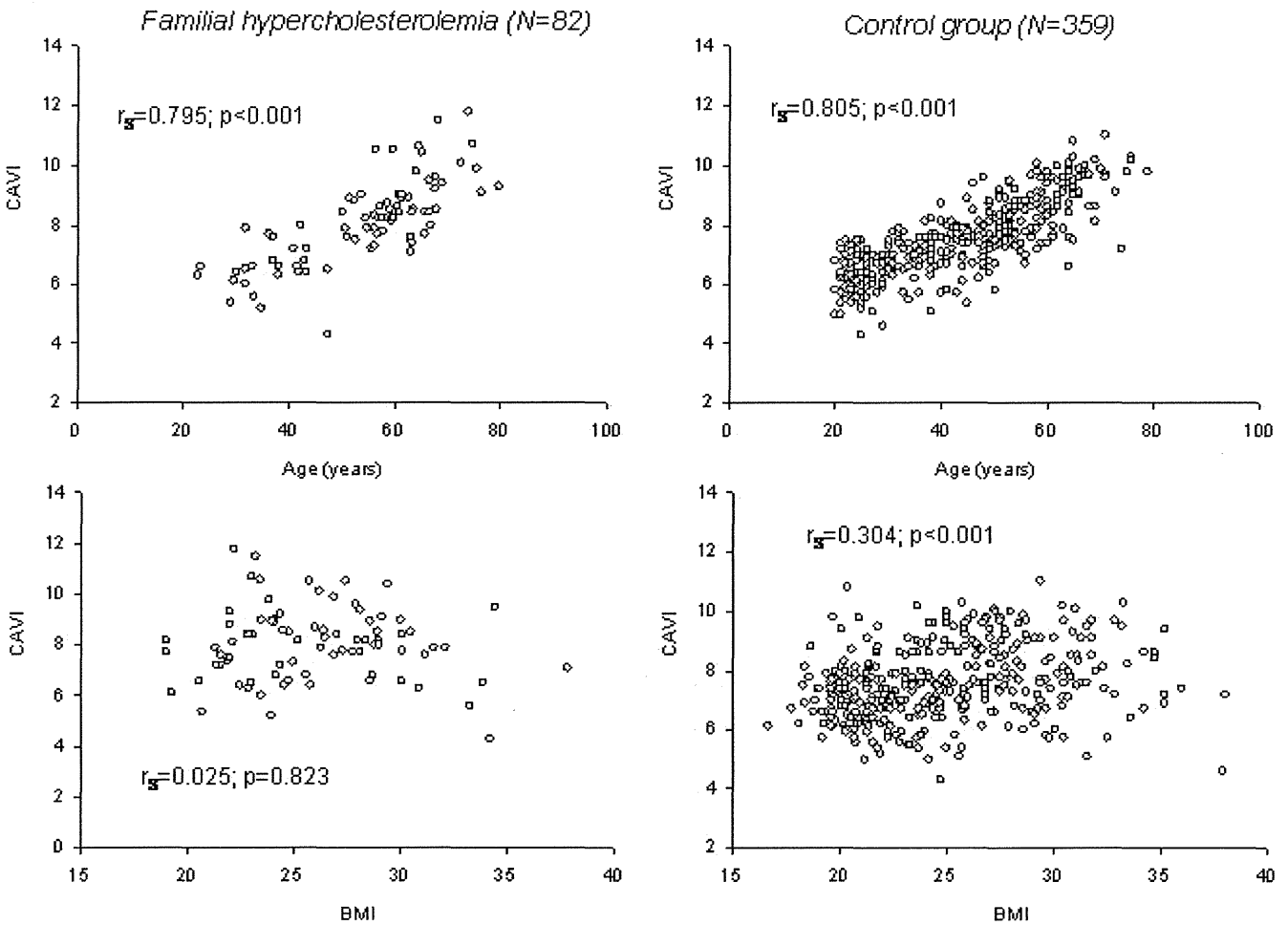

Fig. 2. Spearman's correlation of CAVI with age or BMI in heterozygous familial hypercholesterolemia group and in control group
CAVI: cardio-ankle vascular index; BMI: body mass index; r_S: Spearman's rank correlation coefficient

oxidative stress, which may contribute to the vasoprotective effects[41]. Thus, statins profoundly decrease cardiovascular risk and coronary mortality in patients with heterozygous FH and improve their clinical fate[42-44]. It has been also reported that fluvastatin improves arterial stiffness in patients with coronary artery disease and hyperlipidemia and that pitavastatin decreases CAVI after 12 months of treatment[24, 45]. All FH patients in our study used statins; moreover, 42% were treated with the combination of a statin and ezetimibe. Ezetimibe decreases the plasma level of cholesterol by limiting its absorption in the intestine. Treatment with ezetimibe decreases cholesterol level as well as CAVI[25]. LDL-lowering therapy was sufficient in our group of FH patients since average values of total cholesterol as well as LDL-cholesterol were close to the average values in the Czech population. According to the results of the Czech post-MONICA study, the average values of total cholesterol in the Czech Republic in 2001 were 5.88 ± 1.08 mmol/L in men and 5.82 ± 1.13 mmol/L in women, respectively[46]. Our results showed that, in FH patients with well-controlled risk factors, the progression of atherosclerosis measured by CAVI is not advanced as compared to healthy controls.

There are a few limitations of this study. First, the study was not designed as a case-control study; therefore, the controls were not age- and sex-matched. Nevertheless, the groups did not differ significantly in the distribution of men and women. As the differences in age and BMI are a concern, adjustment for age and BMI is a well-accepted statistical approach for overcoming differences between the study and control populations.

Secondly, it is not possible to evaluate the direct effect of treatment with statins/ezetimibe on CAVI in

patients with FH, since treatment with hypolipidemic drugs was introduced many years earlier than the measurement of CAVI using VaSera® 1500. Moreover, it is not possible to measure CAVI in new FH patients before therapy, since practically all patients have been treated with statins prescribed by their general practitioners before they visit our department to verify the diagnosis of FH. The discontinuation of statins before CAVI measurement for a longer time is not possible for ethical reasons. The direct effect of treatment with pitavastatin as well as ezetimibe on CAVI reduction was recently reported in patients with diabetes mellitus without cardiovascular complications[24, 25].

Thirdly, blood lipid values were not available for the control group and therefore their comparison with the values of FH patients treated with statins was not possible. For an approximate comparison, data from the Czech post-MONICA study were used; blood lipids of a representative sample of the Czech population were examined in this study. Moreover, CAVI had a poor relationship with total cholesterol and LDL-cholesterol levels and no correlations among CAVI and the triglycerides and HDL-cholesterol levels were found[47]. In addition, the aim of this study was not to compare blood lipids of a healthy population and patients with FH treated with statins, but to assess CAVI values in these two groups. Since CAVI is quite a sensitive, non-invasive index of atherosclerosis progression, it might be of help for patients with FH where the risk of premature atherosclerosis development is high.

In conclusion, we demonstrated that there are no significant differences in CAVI between asymptomatic patients with heterozygous FH with well-controlled major risk factors and healthy controls; however, further studies using clinical long-term follow-up are required.

Disclosure

The authors declare no conflicts of interest.

Acknowledgement

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Artificial Organs

Communication

Medical Responses Following the Sendai Quake (East Japan Earthquake, March 11, 2011)

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On March 11, 2011, disaster struck the east coast of Japan (1–7) named of the Great East Japan Earthquake or Sendai Quake (8) (Wikipedia).

Japan had been expecting a large earthquake for a long time. The Sendai Quake involved three epicenters at various distances out to sea. The force of the magnitude 9.0 quake caused an enormous tsunami that deluged the cities on the eastern seashore in the Tohoku area (northeast coast of Japan). In Minamisanriku City, for example, almost all buildings were lost after the earthquake and tsunami struck (Fig. 1).

To add to the disaster, fires broke out after the earthquake and tsunami. Large portions of the cities near the eastern seashore were completely lost. In addition to these disasters, a meltdown occurred at the Fukushima nuclear power plant. Radioactive contamination occurred not only throughout Japan but also all over the world.

Unfortunately, detailed medical data about the aftermath of the Sendai Quake are not available because all medical records were lost with the hospital buildings, especially in the tsunami areas near the eastern seashore. Detailed information of the number of dead has not yet been summarized, even by the Japanese government. As many as 20 000 people have been reported lost as a result of this complex emergency. The medical response following the earthquake and tsunami in eastern Japan has not been clearly described. This short report is intended to provide details of this response.

FIG. 1. Minamisanriku City after the tsunami (photo by the Miyagi Medical Support team).

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MEDICAL RESPONSE TO THE SENDAI QUAKE

The Tohoku University Hospital is located in Sendai City in the area that sustained the most damage from the tsunami and earthquake. Despite the sadness that flooded the nation after the disaster, one consolation was that no fatalities occurred among patients, doctors, nurses, or other staff at the University Hospital. The response to the disaster at this hospital can be examined in four stages.

The first stage involved initial recovery and preparation for dealing with the aftereffects of the disaster. First, the safety of all patients and staff members was secured. Then, medical resources were mobilized according to the hospital's triage tag system. Everything in the University Hospital was rearranged to accommodate disaster victims. All routine surgeries and medical examinations were postponed, and the outpatient clinic was closed. When disaster victims arrived at the University Hospital, they received green, yellow, red, or black tags, according to the methodology of the triage tag system. Patients with green tags were treated in the outpatient clinic, those with yellow tags went to the intensive care unit, those with red tags went to the operating room, and those with black tags went to the building of basic science. Appropriate treatment was delivered in these various locations.

In the second stage, normal hospital functions were restored. Planning began for the acceptance of patients being transferred from damaged hospitals on the eastern coast. Shortages of all medical resources had been anticipated, so messages were sent to all university hospitals in Japan to gather drugs and food and to prepare disaster medical assistance teams.

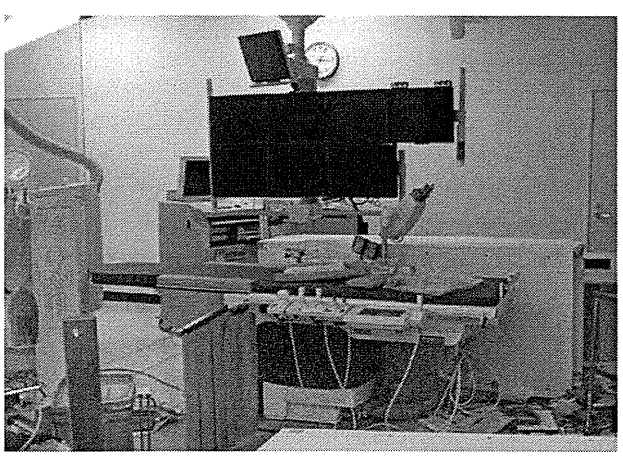

FIG. 2. Cardiac catheterization room after the Sendai Quake.

FIG. 3. Shelter after the tsunami (photo by Miyagi Medical Support Team).

In the third stage, teams of doctors and nurses, along with medical resources, food, and drugs, were sent to the afflicted hospitals. Thousands of medical support teams were sent to the cities on the eastern coast affected by the tsunami. The fourth stage, which involves reconstruction of medical support buildings in the damaged area, is still ongoing.

THE STATE OF MEDICAL CARE AFTER THE TSUNAMI

Challenges were many throughout the region. Creative solutions to various problems had to be sought. For example, in the Miyagi Cardiovascular Respiratory Center, electric power and water supplies were down. Patients in stable condition were therefore discharged, and emergency patients were treated using equipment powered by in-house power generation units.

Despite all the efforts to meet people's needs, medical resources were inadequate because of the magnitude of the disaster. Medical equipment was damaged and debris was everywhere (Fig. 2). Medical teams visited shelters after the tsunami (Fig. 3). The Miyagi Medical Support team diagnosed and treated in a temporary shelter.

An emergency care unit is present at Sendai City Hospital. Although ambulances had been salvaged from the disaster area, destroyed roads and traffic jams prevented them from transporting patients to the hospital. Many patients came to Tohoku Rosai Hospital, located in the city center, on foot. The

volume of patients was large, and the hospital was so busy that medical staff were unable to return to their homes.

Miyagi Shakaihoken Hospital is located near the coast. Many tsunami victims went to that hospital, but the surgery department's systems were down. Patients could not be adequately treated without functional operating rooms.

Some of the most severe damage was observed at Kesennuma City near the seashore. All buildings in that area were destroyed by the earthquake, tsunami, and fire; therefore, people were required to go to refuge centers. Control of hypertension, diabetes, and many other health disorders was difficult in these makeshift conditions, and newly developed electronic doctor's bags were used to control these conditions.

Furthermore, the Sendai Airport was also completely destroyed by the tsunami, but it was restored soon after by the TOMODACHI operation carried out by the US Army.

FUKUSHIMA NUCLEAR POWER PLANT MELTDOWN

The Fukushima nuclear power plant accident exacerbated the already difficult situation in hospitals. On March 11, a meltdown at the power plant was reported, and hydrogen explosions followed on March 12 and 14. Radioactive materials were scattered as a result of these accidents. The plant was shut down.

In Japan, discussion is ongoing concerning the future consequences of the radiation leaks resulting from the accident at Fukushima (9–12). In the early 1960s, Japan experienced a large amount of strontium, cesium, and plutonium fallout caused by atomic bomb experiments conducted by several countries, including the USA, France, the Soviet Union, and China. Plutonium levels in Japan were estimated to be 100 000 times higher in the 1960s compared with recent levels. But the life span of Japanese people is the longest in advanced countries. No one can show the risk of radiation fallout in early 1960s. No increase in cancer incidence was observed in Japan in the early 1960s. Thus, the true risk of radiation fallout is also unclear, because double-blind tests of radiation poisoning cannot be performed.

Sendai City is located north of Fukushima. All roads from Tokyo (south of Fukushima) and other areas of Japan had been blocked between Fukushima and Tokyo, because antinuclear power activists announced a non-scientific propaganda concerning the risk of radiation material fallout. Relief supplies could not be transported into the Fukushima area because of demonstrations by the antinuclear activists. So, the relief goods could not go north to Sendai. Many patients did not survive due to a shortage of drugs and food caused by the propaganda of the antinuclear activists.

USE OF ARTIFICIAL ORGANS DURING THE DISASTER

At the time of the disaster, more than 50 patients were on respirators, whereas 11 were dependent on hemodialysis (HD) at Tohoku University Hospital. Emergency power units ensured the safety of these patients. However, all coastal hospitals had sustained devastating damage. Therefore, all patients who were dependent on HD were transported to Tohoku University Hospital. Medical resources were inadequate to meet their needs, and helicopters transferred these HD patients to other hospitals. Around 100 HD patients were transferred to the other hospitals. In particular, large numbers of HD patients were transferred to Hokkaido.

Three patients required the Nipro ventricular assistance system (VAS) support at Tohoku University Hospital during the Sendai Quake. Because emergency power started smoothly, no disruption of VAS treatment occurred.

However, certain lifelines, such as electric power, water, and gas supplies, had all been shut down in Sendai City. Therefore, patients requiring rotary blood pumps were transported to the ambulance center and subsequently moved to the University Hospital after the roads became passable. Pneumatic VAS remained useful during the disaster, which was surprising because they were situated in the hospital with the emergency power unit.

Patient care had to be performed, although medical resources were limited. For VAS and HD, the prothrombin time and international normalized ratio must be measured. These parameters had to be checked in shelters. For example, the Miyagi Medical Support Team, who visited various shelters, brought electronic medical equipment. This equipment was a lifeline for patients taking refuge in shelters, especially for those requiring life support using artificial organs.

TELEMEDICINE USING THE ELECTRONIC DOCTOR'S BAG

Medical resources were inadequate to respond to the disaster. Medical treatment was limited because all lifelines had been compromised. Doctors and nurses took it upon themselves to visit people in shelters, travelling destroyed roads on foot to do so.

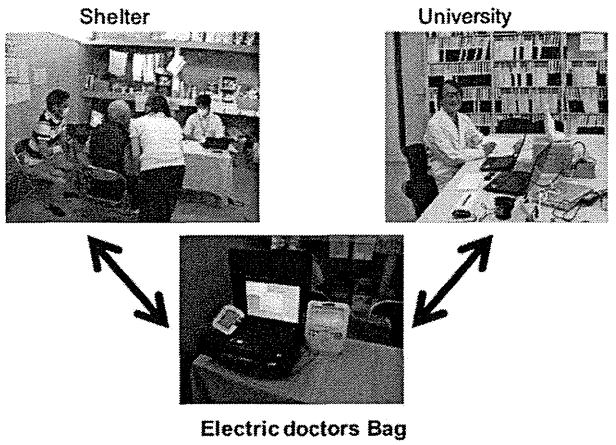

FIG. 4. Above: Clinical application of the electronic doctor's bag in a shelter in Kesennuma City. Below: The bag being tested at Tohoku University.

The electronic doctor's bag, which was invented at Tohoku University, was useful in responding to victims' needs in these emergency conditions (Fig. 4).

The electronic doctor's bag was first used in the shelter in Kesennuma City, one of the most severely damaged areas, after approval from the ethics committee of Tohoku University Graduate School of Medicine. Use of the electronic doctor's bag facilitated evaluation of the condition of patients at the shelter by doctors located at the University. At the time of the disaster, the personnel shortage precluded on-site evaluation. Therefore, telemedicine and remote medicine were thought to be useful. The electronic doctor's bag enabled electrocardiography, blood pressure measurement, and ultrasonic diagnosis to be performed at the disaster shelters. Using this newly developed system, medical personnel in the shelters were also able to confer with doctors at Tohoku University via Skype. Using this device, control of anticoagulation, blood sugar levels, and blood pressure are able to be achieved, thereby preventing adverse cardiovascular events from occurring.

SUMMARY

After the Sendai Quake, all medical resources were mobilized to respond to the disaster. However, shortages of everything caused seemingly insurmountable problems, especially in areas affected by the tsunami. Maintenance of lifelines was vital to patients requiring artificial organs.

Medical equipment preparation and planning are now under way to enable adequate response to future large disasters. Discussion is ongoing about the continued risk of radiation after the Fukushima nuclear power plant meltdown. In previous reports, no risk of increased cancer due to exposure to radiation <100 mSv was reported. In Japan, all radioactive fallout in every area has been reported daily on the governmental website since the disaster. Information about radiation levels is publicly available in Japan.

In conclusion, a detailed statistical analysis of the disaster is now under way, the results of which will be reported in the near future. The most important thing during times of disaster is the rapid recovery of lifelines.

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Focal atrial tachycardia arising from the cavotricuspid isthmus with saw-tooth morphology on the surface ECG: electrocardiographic and electrophysiologic characteristics

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Abstract
Background Limited information is available about focal atrial tachycardia (AT) arising from cavotricuspid isthmus (CTI).
Objective The purpose of this study is to evaluate the electrocardiographic and electrophysiologic characteristics of a focal AT arising from the CTI.
Methods From a consecutive series of 92 patients undergoing radiofrequency catheter ablation (RFCA) for focal AT, three (4.4%) patients (three men) with a focal AT arising from the CTI were studied.
Results The median age was 71 years (range, 50 to 81 years). None of the patients had a history of CTI-dependent atrial flutter. The electrocardiogram (ECG) of a focal AT showed a significant negative F-wave in the inferior leads. Focal AT could be reproducibly initiated and terminated with programmed stimulation. The focus of the tachycardia was localized to the central isthmus in two and the paraseptal isthmus in one patient. The median tachycardia cycle length was 275 ms (range, 260 to 310 ms). In two patients, the focal AT was adenosine insensitive. In all of the patients, tachycardia was entrained from multiple right atrial sites, including the earliest activation site. RFCA was acutely successful in all patients. Long-term success was achieved in all patients over the median follow-up of 18 months (range, 6 to 33 months).
Conclusions Cavotricuspid isthmus is an uncommon site of origin for focal AT. This focal AT has unique electrocardiographic characteristics such as saw-tooth morphology on ECG and is suggested to be caused by a focal reentrant circuit located at the CTI. Long-term success is achieved with focal ablation.

Keywords Cavotricuspid isthmus · Atrial tachycardia · Saw-tooth morphology · Catheter ablation · Electro-anatomical mapping

1 Introduction

It is well recognized that there is a characteristic anatomical distribution for focal atrial tachycardia (AT). In the right atrium (RA), foci tend to occur along the crista terminalis [1], around the tricuspid annulus [2], and in the para-hisian region [3]. However, there is little information about focal AT arising from cavotricuspid isthmus (CTI). The purpose of this study is to characterize the electrocardiographic and electrophysiologic characteristics of focal AT arising from CTI.

2 Methods

The study population included three patients from a consecutive series of 92 patients undergoing radiofrequency

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catheter ablation (RFCA) for focal AT between February 2002 and April 2010. All patients had clinically documented paroxysmal or incessant-type AT. All antiarrhythmic drugs were ceased a minimum of five half-lives before the procedure. Written informed consent was obtained from all patients prior to the procedures.

A 5-French octopolar catheter was positioned in the coronary sinus, a 6-French 20-pole catheter was placed along the tricuspid annulus and a 5-French four-pole catheter was placed in the right ventricular apex. A 7-French 4- or 8-mm-tip catheter (Navistar) was inserted via the femoral vein for atrial mapping, pacing, and ablation.

Standard electrophysiological criteria were used to diagnose AT [4]. Induction of AT was made by atrial programmed extrastimulation and burst atrial pacing. If AT was not occurring, isoproterenol was infused (1 to 5 μg/min). Bipolar electrograms were filtered at a bandpass setting of 30–500 Hz and recorded digitally. Pacing was performed using a stimulator. The atrial mapping was performed during tachycardia to identify the earliest atrial activation site. In all patients, an activation mapping was created using electro-anatomical mapping system (CARTO; Biosense Webster). Entrainment pacing from CS ostium, low lateral right atrium, and earliest activation site was performed in all patients. A radiofrequency catheter ablation was performed to achieve a target temperature of 52°C for a maximum power of 25 W. An irrigation tip catheter was not used. Procedural success was defined by the absence of spontaneous or inducible tachycardia over a period of 30 min following RFCA despite programmed stimulation and burst atrial pacing. Values are given as median and range.

3 Results

3.1 Patient characteristics

Of the 92 patients who underwent RFCA for focal AT, three patients (3.2%) were determined to have a focal AT arising from the cavotricuspid isthmus. All patients were males (median, 71 years; range, 50 to 81 years). Symptom duration to tachycardia had been present for a median of 4 months (range, 3 to 8 months). Patients had taken a median of one (range, 0 to 1) antiarrhythmia drugs. One patient had a dilated cardiomyopathy. The left ventricular ejection fraction was a median of 55% (range, 37% to 57%). The left atrial size was a median of 23 mm (range, 23 to 28 mm). None of the patients had any prior history of atrial flutter, previous catheter ablation for atrial flutter, or previous cardiac surgery. All patients had a 12-lead electrocardiogram (ECG) performed during AT. The ECG pattern during AT masqueraded as common atrial flutter. The ECG of AT arising from CTI had an isoelectrical line. However, an isoelectrical line was obscured in the ECG of AT arising from CTI at 2:1 conduction as shown in Fig. 1. The ECG of a focal AT showed a significant negative F-wave with saw-tooth morphology in the inferior leads.

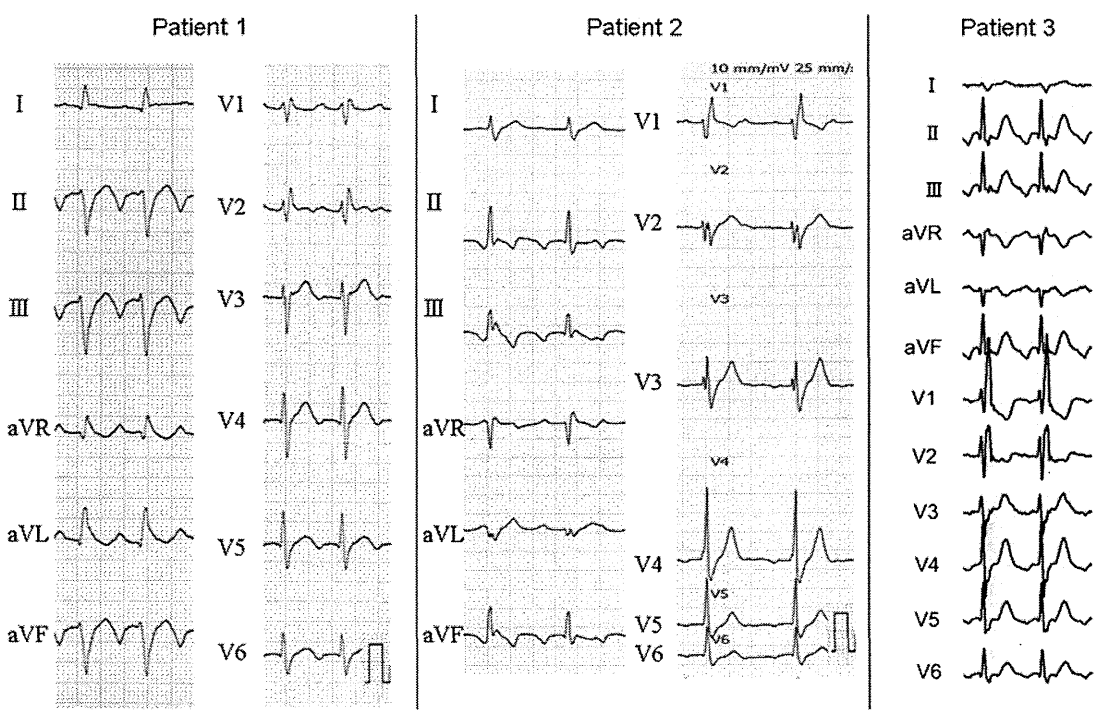

Fig. 1 Twelve-lead ECG of atrial tachycardia arising from cavotricuspid isthmus was shown here. In the inferior leads, a significant negative F-wave with saw-tooth morphology was recognized in all patients

3.2 Characteristics of the tachycardia

The characteristics of the tachycardia were shown in Table 1. During the study, tachycardia was not occurred spontaneous onset/termination in spite of infusion of isoproterenol. In all patients, AT was induced by atrial burst pacing or atrial programmed extra-stimuli. Sustained tachycardia was present in all patients with a tachycardia cycle length of a median of 275 ms (range, 260 to 310 ms). In all patients, AT could be differentiated from atypical AVNRT and permanent form of junctional reciprocating tachycardia by the presence of permanent or transient AV dissociation.

Activation mapping by electro-anatomical mapping was obtained during tachycardia in all patients. AT was presented in a centrifugal activation pattern (Fig. 2). The earliest atrial activation site was within the cavotricuspid isthmus, and activation mapping localized the tachycardia to the paraseptal isthmus in one, and to the central isthmus in two patients. Adenosine (20 mg) was infused in two patients. The other patient was not performed because of a history of asthma. In two patients, adenosine was not effective, that is, high-degree atrioventricular block occurred after administration of adenosine (20 mg), but the tachycardia was not terminated and the tachycardia cycle length and activation sequence was not changed (Fig. 3). Entrainment was performed from multiple atrial sites (coronary sinus ostium, low lateral right atrium, or earliest activation site). Post-pacing interval was longer than the tachycardia cycle length at the coronary sinus ostium and the low lateral right atrium (Fig. 4). Post-pacing interval was equal with the tachycardia cycle length at the earliest activation site with concealed entrainment (Fig. 5).

3.3 Radiofrequency catheter ablation

Radiofrequency catheter ablation was performed and acutely successful in all patients. During RFCA, catheter was not moved or dragged. At the site of successful ablation, the endocardial atrial activation preceded the coronary sinus ostium by a median of 62 ms (range, 47 to 65 ms). The electrogram at the successful site was fractionated potential or double potential in all patients (Figs. 5 and 6). The median duration of fractionated potential at the earliest activation site was 112 m (range, 79 to 117 ms), and the peak-to-peak amplitude at the earliest activation site was median 0.38 mV (range, 0.37 to 0.45 mV). The median number of RFCA was three applications (range, 1 to 3). After beginning RFCA, tachycardia was terminated at the mean time of 10 s. In two patients, ablation was performed in a 4-mm-tip catheter and in one patients, ablation was performed in an 8-mm-tip catheter. The mean ablation time was 220 s (range, 90 to 240 s). There were no procedural complications. Long-term success was achieved in all patients over a median follow-up of 18 months (range, 6 to 33 months).

4 Discussion

4.1 Major findings

Past studies have reported that in the right atrium (RA), foci tend to occur along the crista terminalis [1], around the tricuspid annulus [2], and in the para-hisian region [3] and in the left atrium (LA), foci tend to occur around the mitral annlus [5] and pulmonary vein [6]. But only limited studies describing the focal AT arising from the cavotricuspid isthmus was available [7]. The present study demonstrates the electrocardiographic and electrophysiologic characteristics in patients with focal AT arising from the cavotricuspid isthmus.

4.2 Electrocardiographic characteristics

In the electrograms of focal AT arising from CTI, the characteristic point was that the morphology of the ECG during focal AT arising from CTI was similar to that of typical atrial flutter (AFL). Balbato et al. described that typical AFL ECG was a good predictor of CTI-dependent AFL, but in about 10% of typical AFL ECG, a non-CTI AFL was identified [8, 9]. Waldo and Okumura et al. described that the surface ECG of atrial flutter was dependent on the activation sequence of the LA [10]. Past

Table 1 Characteristics of the tachycardia

Patient no.	Age/ gender	TCL (ms)	Mode of tachycardia initiation/termination	Location on cavotricuspid isthmus	Adenosine	EGM Duration at earliest site (ms)	EGM amplitude at earliest site (mV)	Percentage of the TCL covered by mapping around the TA
1	50/M	260	Programmed stimulation	Paraseptal isthmus	20 mg NE	117	0.45	37%
2	71/M	275	Programmed stimulation	Central isthmus	NA	79	0.37	43%
3	81/M	310	Programmed stimulation	Central isthmus	20 mg NE	112	0.38	31%

TCL tachycardia cycle length, *TA* tricuspid annulus, *NE* not effective, *NA* not application

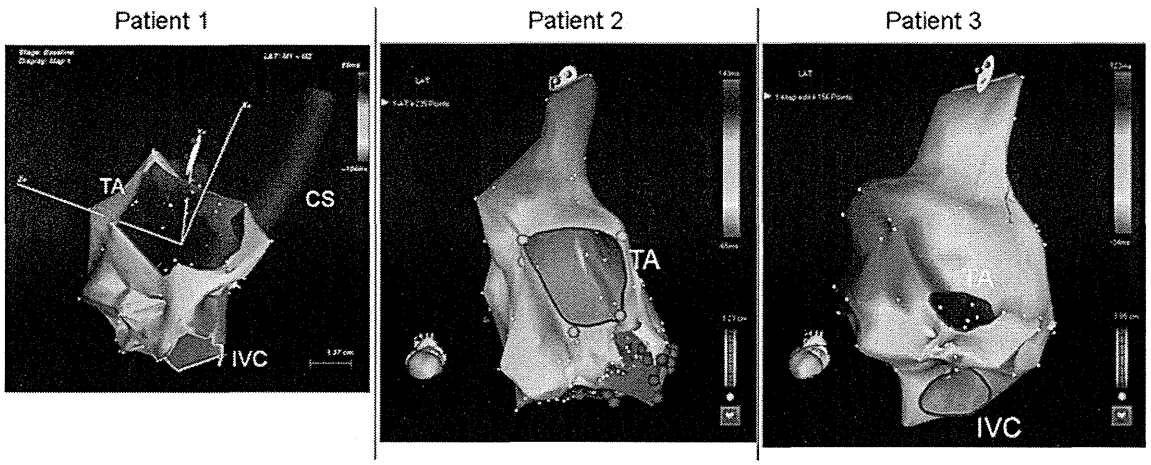

Fig. 2 The activation mapping showed the focal pattern of the right atrium during atrial tachycardia arising from the cavotricuspid isthmus of three patients. In patient no. 1, the activation was propagated centrifugally from the paraseptal isthmus. In patient no. 2 and 3, the activation was propagated centrifugally from the central isthmus. *Orange dots* represent tricuspid annulus points. *Gray dots* represent scar area points. *TA* tricuspid annulus, *IVC* inferior vena cava, *CS* coronary sinus

studies have demonstrated different patterns of coronary sinus (CS) activation in counterclockwise AFL and clockwise AFL [11]. In counterclockwise AFL, left atrium was activated predominantly over the CS ostium and inferior-to-superior activation of left atrium was formed in the shape of negative saw-tooth morphology in the inferior leads. In contrast, in clockwise AFL, the left atrium was activated predominantly over the Bachmann's bundle and superior-to-inferior activation of the left atrium was appeared as the shape of a positive deflection in flutter wave in the inferior leads. In the present study, we hypothesized that the CTI reentrant circuit was closer to the CS ostium than the Bachmann's bundle. Therefore, we thought that the surface ECG during focal AT arising from CTI was similar to that during typical AFL.

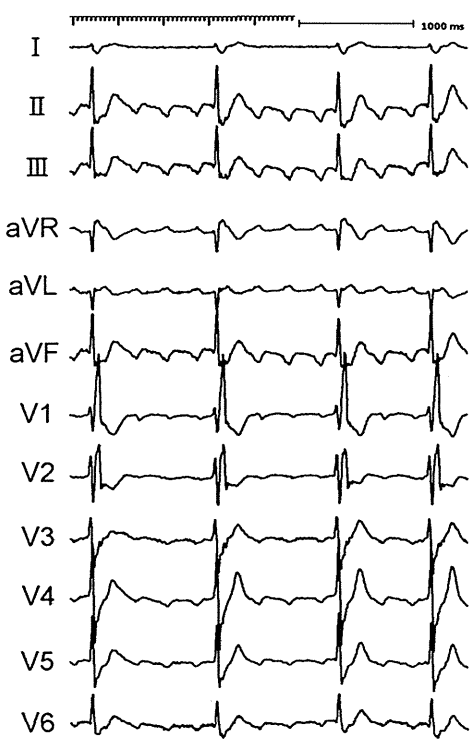

Fig. 3 After adenosine 20 mg, high-degree atrioventricular block occurred, but the tachycardia was not terminated and the tachycardia cycle length and activation sequence was not changed

4.3 Electrophysiologic characteristic

In the present series, the CTI was the site of focal AT origin in three of 92 patients (3.2%). Focal AT was defined as atrial activation starting rhythmically in a small area from which it spread out centrifugally. It has been demonstrated that different mechanisms may cause focal AT such as triggered activity, enhanced automaticity, or micro-reentry. In the present study, focal AT could be initiated and terminated by programmed stimulation. Furthermore, tachycardia could be entrained from the earliest activation site, CS ostium and low lateral RA. These phenomena were assumed micro-reentry. Markowitz et al. described that the characteristics of adenosine-insensitive focal AT differed from adenosine-sensitive AT and were consistent with small reentrant circuits [12]. They concluded that focal re-entry was a mechanism of AT in adenosine-insensitive focal AT. In this present study, focal AT was adenosine insensitive in two patients, and adenosine was not infused due to a history of asthma in the third patient. These data supported that the mechanism of focal AT arising from CTI was micro-reentry. Groot et al. described that the area around the site of the earliest activation of focal AT was characterized by an increased incidence of fractionated potentials, a prolonged duration and lower peak-to-peak amplitude [13]. The high-

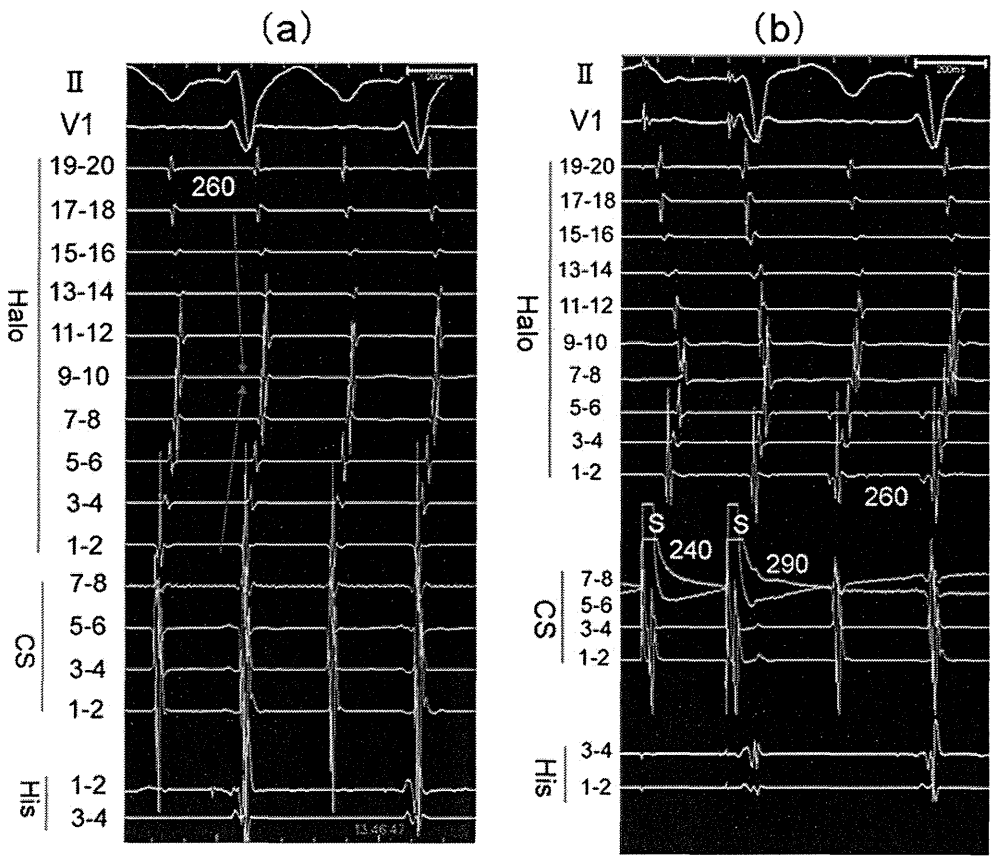

Fig. 4 Entrainment of focal atrial tachycardia from patient no. 1. (**a**) The electrogram activation sequence along the tricuspid annulus showed simultaneous activation pattern during atrial tachycardia. (**b**) Pacing from coronary sinus ostium, and entrainment demonstrates a post-pacing interval (PPI) 30 ms longer than the tachycardia cycle length (TCL)

degree of fragmented potential indicated that poor cell-to-cell coupling was present and poor cell-to-cell coupling was thought to include a conduction abnormality. In the present study, a prolonged duration and low amplitude of fragmented or double potential were observed at the earliest activation site. These findings also indicated mirco-re-entry as underlying mechanism of focal AT arising from CTI.

Recently, Yang et al. described the electrophysiological characteristics of intra-isthmus reentry [14, 15]. They revealed that the circuit of intra-isthmus reentry was within

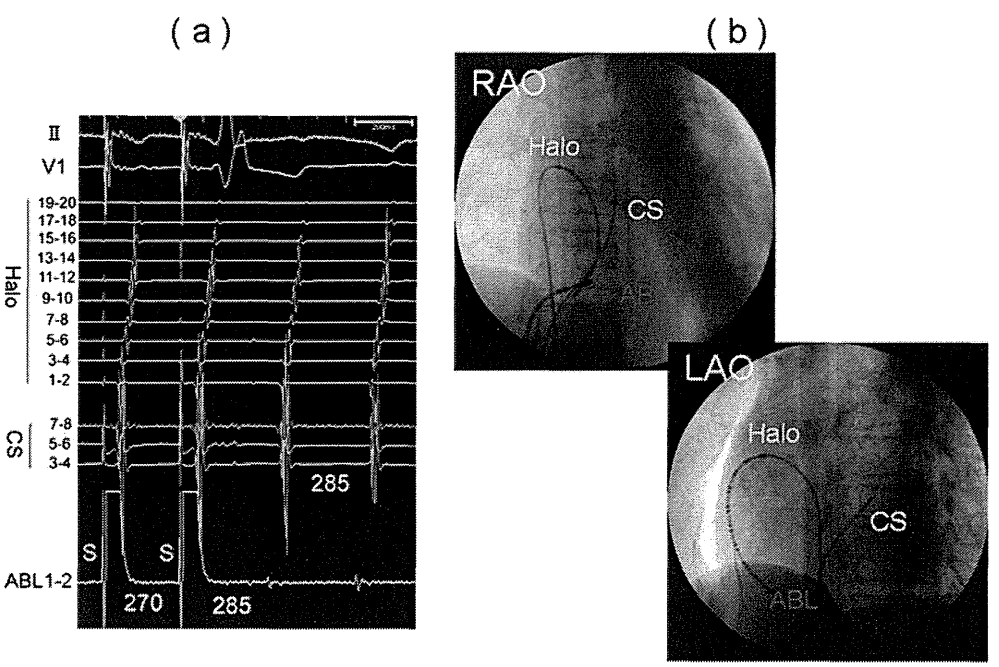

Fig. 5 Entrainment of focal atrial tachycardia from patient no. 2. (**a**) Pacing from the earliest site at the central isthmus resulted in a PPI equivalent to the TCL of 285 ms. The morphology of electrograms in Halo and coronary sinus (*CS*) were same during entrainment pacing and tachycardia. (**b**) Right anterior oblique and left anterior oblique fluoroscopic views of mapping and ablation catheters. In this case, successful ablation was performed with an ablation catheter positioned at central isthmus. *CS* coronary sinus

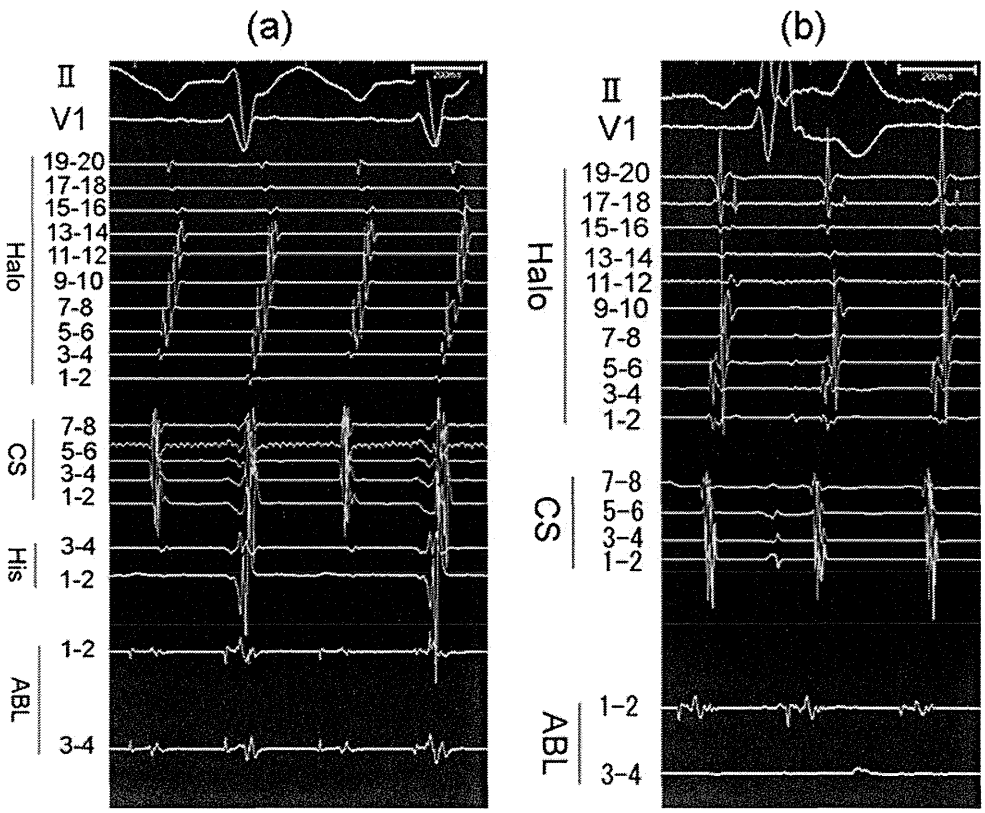

Fig. 6 The electrograms from the successful ablation site in patient no. 1 and 3. (**a**) In patient no. 1, the electrogram recorded at the earliest activation site was fractionated and 65 ms ahead of the atrial potential at the coronary sinus ostium. (**b**) In patient no. 3, the electrogram recorded at the earliest activation site was fractionated and 62 ms ahead of the atrial potential at the coronary sinus ostium

the region of septal, mid-, and anteroinferior CTI region and the successful site of ablation for the intra-isthmus reentry circuit was the longest duration of fractionated potential with concealed entrainment. The most important difference between our study and their report is that all of the cases in our study were initial ablation cases whereas at least half of their cases had received at least one prior ablation treatment for AFL.

It was important to differentiate between focal AT arising from CTI and focal AT arising from tricuspid annulus. McGuire et al. reported the existence of cells with nodal-like characteristics around the entire tricuspid annulus [16]. These cells resembled the nodal cells in terms of their cellular electrophysiology, response to adenosine, and lack of connexine 43. It was suggested that these cells might be the substrate of the focal AT from the tricuspid annulus [2]. In the present study, there were no effects of adenosine in the focal AT and at the earliest activation site, only atrial potential was observed and ventricular potential was not seen. These findings were thought to be compatible with the focal AT arising from CTI.

4.4 Study limitation

Because of the relatively small number of cases in our study, it will be necessary to confirm our findings on a larger scale in the future.

It is important to distinguish between AT arising from CTI and typical atrial flutter. Most of the characteristics (induced with programmed stimulation, adenosine insensitive, and good entrainment at CTI) are also found in typical atrial flutter. However, AT arising from CTI could be distinguished from typical atrial flutter based on the following three reasons; first, AT arising from the CTI showed a focal centrifugal activation pattern on the CARTO activation map. And the earliest activation site was within the CTI in AT arising from CTI. Second, the intracardiac activation sequence was a simultaneous pattern defined as symmetrical activation of septal and lateral RA annulus site in two AT patient arising from CTI as shown in Fig. 6. This simultaneous activation pattern was not seen in typical atrial flutter. Third, post-pacing interval (PPI) was equal with the tachycardia cycle length (TCL) at CS ostium and low lateral RA in typical atrial flutter. However, PPI was longer than the TCL at CS ostium and low lateral RA in all patient of AT arising from CTI as shown in Fig. 4. This also provides evidence for distinguishing AT arising from CTI from typical atrial flutter.

5 Conclusions

Cavotricuspid isthmus is an uncommon site of origin for focal AT. This focal AT has unique electrocardiographic