and hs-CRP levels. Desacyl-ghrelin is a fast-acting hormone that is secreted from the stomach and plays a role in initiatiing eating. Its plasma concentrations are elevated before a meal under negative-energy conditions and lowered after a meal[22, 23]. In this study, plasma desacyl-ghrelin concentrations were within the physiological range and there was no difference between boys and girls.

Hs-CRP is considered to be an inflammatory marker because it shows a close association with cardiovascular disease in clinical studies[24]. Hs-CRP is found in the liver, monocytes, macrophages, and adipose tissue, and its level is negatively correlated with adiponectin in adipose tissue[25, 26]. It was no surprise that the hs-CRP level was within the normal range in our participants.

Marker for Visceral Fat Accumulation

Visceral obesity (i.e., PFT) was assessed by ultrasonography and even with hand-held equipment; this technique was appropriate to determine PFT. From multivariate regression analysis, using PFT as a dependent variable and other factors as independent variables, it was revealed that leptin and TG were independently associated with PFT in boys and leptin was independently associated with PFT in girls. As the production of leptin is known to depend on the amount of adipose tissue, it is unsurprising that leptin levels are higher in girls because they usually have more fatty tissue than boys. The measurement of other surrogate markers for visceral fat accumulation is needed to more precisely determine the mechanisms that regulate PFT.

In previous studies, PFT was positively correlated with the visceral fat area determined by CT and we defined visceral obesity as PFT >8 mm[8]. Some studies have reported cut-off values for PFT that are very close to ours. One study performed in adults[27] used receiver operating characteristic (ROC) curve analysis and reported cut-off values of 6.1 mm in men and 8.7 mm in women. In a study of school children[28], the cut-off values for PFT were 4 mm for junior high school boys and 8 mm for junior high school girls. In both studies, visceral adiposity in men corresponded to smaller PFT values than in women.

Waist circumference and the waist to height ratio are well-known predictors for cardiovascular disease risk[29], and the Japanese Society of Pediatrics criteria for metabolic syndrome include abdominal obesity, defined as waist circumference >80 cm and/or a waist to height ratio >0.5. We found that PFT was positively correlated with waist circumference and the waist to height ratio in both sexes and, when we estimated waist circumference with a calculated regression line, the PFT of 8 mm corresponded to a waist circumference of 78 cm in boys and 76 cm in girls, values that are very close to the established criteria. Assessments of abdominal fat distribution have recently been reported for infants, and the measurement of PFT is a reproducible method for investigating fat accumulation in early life[30]. Based on these results, PFT could be a good indicator of actual visceral fat accumulation.

Visceral Fat Accumulation

In the present study, even in healthy high school students who do regular exercise, visceral obesity was found in 9.6% of participants (10.3% boys and 9.8% girls). Of note, boys with visceral adiposity exhibited hyperinsulinemia, hyperlipidemia, liver dysfunction and hyperuricemia, in addition to other risk factors for atherosclerosis. Puberty is a period of rapid growth associated with hormonal, metabolic and body composition changes; therefore, the effect of puberty on insulin sensitivity is quite interesting. One report of randomly selected subjects aged 14–19 showed that fasting insulin peaked at age 16 and subsequently declined in both sexes, and the prevalence of metabolic syndrome (MetS) was highest in those aged 16–17 years[31]. Another study reported decreased insulin sensitivity in obese subjects mid-puberty, which had returned to pre-pubertal levels by the end of puberty[32]. We speculated that the elevated FIRI in those aged around 16 years may strongly contribute to insulin sensitivity and visceral fat accumulation. In our study, there was no significant difference in basal FIRI between sexes, but boys with visceral fat accumulation had higher FIRI. It is possible that adolescents with higher FIRI are more likely to develop fat accumulation and ultimately insulin resistance.

The fact that boys with visceral fat accumulation had higher ALT, lower LpL mass and lower adiponectin levels is also of particular interest. ALT is known to be related to the prognosis of cardiovascular disease and insulin resistance, particularly in men[33], and lower LpL mass with visceral fat accumulation and decreased adiponectin levels are also known to modulate endothelial inflammatory responses in diabetes, obesity and cardiovascular disease[12, 34, 35]. In this study, elevated liver enzymes may reflect inflammation that damages insulin signaling in the liver, and lower LpL mass and adiponectin may induce endothelial inflammatory responses.

The reason why male subjects with visceral fat accumulation exhibit numerous risk factors for atherosclerosis is still unknown. In our previous study, a

positive correlation between PFT and coronary stenosis and lipid disorders was found only in non-obese male subjects[36]. One possibility is hormonal effects. The rapid increase of testosterone in puberty is known to cause insulin resistance, and testosterone and its metabolites were reported to suppress adipocyte production and adiponectin levels[37] in males. In addition, the expression of androgen receptors and glucocorticoid receptors is reported to be greater in visceral adipocytes than in subcutaneous adipocytes[38], and androgens are known to decrease adiponectin levels[39]. Accordingly, these factors may influence the development of atherosclerosis in males and it is clear that the prevention of fat accumulation, especially in boys, is essential to protect against atherosclerosis.

In this study, only two boys and no girls fulfilled the criteria of metabolic syndrome for adults. We also surveyed 186 students (71 boys and 115 girls) about their meals, exercise and leisure time activities, and tried to elucidate the tendency towards visceral obesity (data not shown). We found that students who do not regularly have breakfast, do insufficient exercise, or who play video games for long periods of time showed an increased tendency toward visceral obesity.

Fatty Liver

In Japan, the number of people undergoing health checkups and being diagnosed with fatty liver has been increasing since the 1980s, and has almost doubled within the last 10 years[40]. The frequency of fatty liver is higher in men than in women and is most commonly found in patients with excessive alcohol intake and excessive intake of carbohydrates[41]. In those aged less than 20 years, the frequency of fatty liver is approximately 20% in men and 5% in women[42]; however, in our study, hepatorenal echo contrast positivity, regardless of obesity, was found in 23.3% of boys (32 participants) and 30.4% of girls (55 participants).

Non-alcoholic steatohepatitis (NASH) has recently become acknowledged as a potential cause of liver damage and is closely associated with MetS with excess lipid accumulation in apparently healthy people[43, 44]. In this study, neither alcohol intake nor any specific background was found among students but we do not know why more girls more commonly showed hepatorenal echo contrast. Generally, the definitions of fatty liver assessed by pathological methods and sonographic methods differ. Fatty change of the liver is defined as more than 5% of hepatocytes containing lipids while fatty liver is defined as more than 25% of hepatocytes containing lipids on histopathological diagnosis. By contrast, on ultrasound, fatty change of the liver is defined as more than 10% of hepatocytes containing lipids, and fatty liver is defined as more than 30% of hepatocytes containing lipids[45]. Therefore, this means that fatty change of the liver diagnosed by ultrasound includes livers in which more than 10%, but less than 30%, of hepatocytes contain lipids. Accordingly, it is possible that we included these areas in the hepatorenal contrast-positive group.

Liver biopsy is currently the most sensitive test in patients with NASH to exclude steatohepatitis, but is difficult to perform as part of routine screening. Instead, abdominal ultrasonography offers an alternative, non-invasive approach that can be used for early detection of NASH and MetS.

The boys who showed hepatorenal echo contrast positivity had statistically higher values of waist circumference, waist to height ratio, γ-GTP, FIRI and leptin. In particular, γ-GTP has been reported as an independent risk factor for cardiovascular disease and, in a prospective clinical trial, it could be used as a predictor of hepatic insulin resistance[46, 47]. In a study of MetS-free middle-aged Japanese men, higher γ-GTP levels were found to be a significant risk factor for both MetS and type 2 diabetes[48]. We speculated that boys with fatty liver and higher γ-GTP and FIRI levels could be more prone to developing insulin resistance.

Furthermore, higher values of LpL mass were observed in the hepatorenal echo contrast-positive group than in the hepatorenal echo contrast-negative group in both sexes (**Table 6**). As the plasma LpL mass and hepatic LpL mRNA levels were reported to be significantly higher in morbidly obese patients[49], higher LpL mass may cause fatty change with a higher capacity for resolving triglycerides; however, when we tried to evaluate the differences between the hepatorenal echo contrast-positive group, with or without visceral fat accumulation, and the hepatorenal echo contrast-negative group of boys, we found that boys with hepatorenal contrast positivity and visceral fat accumulation (PFT >8 mm) were the most metabolically affected (**Table 7**) and had the lowest LpL mass, in addition to hypoadiponectinemia. Saiki *et al.* have also reported that low LpL mass was markedly involved in metabolic syndrome and might reflect systemic oxidative stress[13]. Clinically, fatty liver does not always coexist with visceral obesity; therefore, the regulation of fat accumulation in the liver and in adipose tissue appears to involve different mechanisms. Although the number of participants in this study was relatively small, it is unlikely to affect our conclusion that the coexistence of fatty changes of the liver and fat accumulation are atherosclerotic risk factors that need con-

tinued evaluation.

Limitations

The number of participants was small and all participants were volunteers who wished to undergo health checkups. Because all participants were Japanese, generalizability to the non-Japanese population is limited. Visceral-type obesity was defined by ultrasonography.

Conclusion

We tried to determine the risk factors of atherosclerosis in apparently healthy high school students and found a marked difference in the frequency of visceral obesity and fatty liver between boys and girls. Boys with visceral obesity and with fatty liver exhibited stronger associations with risk factors for atherosclerosis. Physical examination of high school students is important to allow for early detection of atherosclerosis and prevent its progression and associated complications.

Acknowledgments

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Original Article

Impact of having One Cardiovascular Risk Factor on Other Cardiovascular Risk Factor Levels in Adolescents

Masao Yoshinaga[1], Hideto Takahashi[2], Masaki Shinomiya[3], Ayumi Miyazaki[4], Nobuichi Kuribayashi[3], and Fukiko Ichida[5]

[1]Department of Pediatrics, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan
[2]Department of Epidemiology and Biostatistics, School of Medicine, University of Tsukuba, Ibaraki, Japan
[3]Chiba Medical Association, Chiba, Japan
[4]Department of Pediatrics, Shakaihoken Takaoka Hospital, Japan
[5]Department of Pediatrics, Graduate School of Medicine and Pharmaceutical Science for Research, University of Toyama, Toyama, Japan

Aim: **Little is known about the impact of having one cardiovascular (CV) risk factor on the levels of other CV risk factors in the general adolescent population. We hypothesized that when adolescents have one CV risk factor, the levels of other CV risk factors worsen simultaneously.**
Methods: **Subjects consisted of 1,257 healthy adolescent volunteers (549 males and 708 females) aged 15–18 years. Abdominal obesity, hypertension, raised triglyceride levels, decreased HDL-cholesterol levels and hyperglycemia were used as CV risk factors. Homeostasis assessment of insulin resistance (HOMA-IR) was used as a surrogate marker of insulin resistance. Levels of four biomarkers, leptin, adiponectin, high-sensitive C-reactive protein, and desacyl-ghrelin, were also determined. Cut-offs for gender-specific individual CV risk factor levels were based on the 90th (or 10th) percentile values of the subjects in the present study.**
Results: **The levels of all CV risk factors and HOMA-IR significantly and simultaneously worsened when adolescents had one CV risk factor in both genders. Having any one CV risk factor indicated the development of other CV risk factors in adolescents; in particular, we found that the development of abdominal obesity in male subjects had a harmful effect on the levels of other CV risk factors and was associated with the worsening of all four biomarkers examined.**
Conclusions: **It is important to determine the presence or absence of these CV risk factors before and/or during adolescence, because having one CV risk factor indicates the start of an accumulation of CV risk factors in the general adolescent population.**

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Key words; Cardiovascular diseases, Risk factors, Adolescent, Prevention

Introduction

The prevalence of overweight and obesity in children is increasing rapidly, and the ongoing obesity epidemic represents a major public health burden worldwide[1, 2]. Obesity accompanies a clustering of cardiovascular (CV) risk factors, including abdominal obesity, impaired glucose tolerance, hypertension, and dyslipidemia, which have been collectively termed metabolic syndrome in both children and adults[3-6].

It is well known that an increase or decrease in the number of CV risk factors is strongly associated with the improvement or worsening of individual CV risk factors[7-12]; however, little is known about whether having one CV risk factor has a harmful effect on the levels of other CV risk factors in the general adolescent population. We hypothesized that when adolescents have one CV risk factor, the levels of other CV risk factors worsen simultaneously. This could have important implications for the prevention of CV risk

Address for correspondence: Masao Yoshinaga, Department of Pediatrics, National Hospital Organization Kagoshima Medical Center, 8-1 Shiroyamacho, Kagoshima 892-0853, Japan
E-mail: m-yoshi@biscuit.ocn.ne.jp
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factors in adolescents. Another problem in the pediatric field is that it is difficult to determine the cutoffs for CV risk factors using their CV outcomes for children and adolescents[13], because there have been few long-term longitudinal studies from children to the middle-aged or even the elderly. Many pediatric investigators have used the 90th percentile values for cutoffs of the CV risk factors in children and adolescents[13]. The sample volume of the present study was relatively large for an adolescent study; we determined the 90th percentile values of the CV risk factors based on the data of the present study and used them as the cutoffs for the CV risk factors in the present study.

The aim of the present study was to determine the association between having one CV risk factor and the levels of other CV risk factors in healthy adolescent volunteers.

Methods

Subjects

Subjects consisted of 1,358 healthy adolescent volunteers (587 males and 771 females) aged 15–18 years, who participated in the project between 2006 and 2008. The aim of the project was to establish criteria for CV risk factors in Japanese adolescents. The project was conducted in three areas: Toyama, Chiba, and Kagoshima prefectures. The project was announced through local boards of education in all three areas and all subjects gave written informed consent. Of the 1,358 subjects, 101 were excluded from the study; 52 participated in the project twice and data for only the first visit were used, and 49 had incomplete data. Therefore, 1,257 volunteers were included in the present study (549 males and 708 females). We obtained permission to use and analyze these data from the Ethics Committee of the National Hospital Organization Kagoshima Medical Center under the condition that the confidentiality of all personal data would be maintained. The prevalence of a body mass index (BMI) <25, $\geq 25-<30$, and ≥ 30 was 91.7%, 6.3%, and 2.0% in male subjects, and 95.2%, 4.3%, and 0.6% in female subjects, respectively. The prevalence of BMI <25, $\geq 25-<30$, and ≥ 30 in the Japanese adolescent population was 88.0%, 8.9%, and 3.1% in males, and 90.9%, 7.4%, and 1.7% in females, respectively, in 2006–2008 from the Annual Report of School Health Survey[14], indicating that the prevalence of obese subjects in the present study was lower than in the Japanese general adolescent population.

Physical and Blood Biochemical Parameters

Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg. BMI was calculated as (weight in kg)/(height in m)^2. Blood pressure was measured three times after 10 minutes rest in the sitting position using an automated oscillatory system (TM-2571; A&D Co. Ltd, Tokyo, Japan) and the mean value of the second and third measurements was used. Waist circumference was measured at the umbilical level to the nearest 0.1 cm.

Blood samples were collected in the morning after an overnight fast for estimation of serum levels of high-density lipoprotein (HDL)-cholesterol, triglyceride, fasting blood glucose (FBG) and fasting insulin. HDL-cholesterol levels were determined by a direct quantitative assay. Triglyceride and FBG levels were determined by enzymatic assays. HDL-cholesterol, triglyceride and FBG levels were analyzed using an automated analyzer (JCA-BM9030; JEOL Ltd., Tokyo, Japan). Insulin levels were measured by a chemiluminescence immunological assay using an automated analyzer (Lumipulse® PrestoII; Fujirebio Inc., Tokyo, Japan). All assays were performed at a laboratory (SRL Inc., Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR)[15] was used as a surrogate marker for insulin resistance, and HOMA-IR was calculated as [fasting insulin (μU/mL)] × [fasting glucose (mg/dL)]/405. To evaluate pancreatic β-cell function, we measured HOMA-derived β-cell function (HOMA-β)[15] as [360 × fasting insulin (μU/mL)]/[fasting glucose (mg/dL) − 63].

Leptin, adiponectin, high sensitive C-reactive protein (hs-CRP) and desacyl-ghrelin, levels were measured at the same laboratory (SRL); these adipocytokines and/or inflammatory markers are hereafter collectively referred to as biomarkers. Leptin was measured by a Human Leptin RIA KIT® (Linco Research Inc., St Charles, MO), adiponectin was measured by a Human Adiponectin ELISA kit® (Otsuka Pharmaceutical Inc., Tokyo, Japan), hs-CRP was measured by N-Latex CRP II® (Dade Behring Inc., Marburg, Germany), and desacyl-ghrelin was measured by Desacyl Ghrelin ELISA® (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan).

Definition of CV Risk Factors

Abdominal obesity, hypertension, raised triglyceride levels, decreased HDL-cholesterol levels and hyperglycemia were used as the CV risk factors in the present study. Because the prevalence of obese subjects in the present study was lower than the adolescent population, as cited above, gender-specific cut-offs were determined after adjustment for the weighted mean of the BMI distribution (BMI <25, $\geq 25-<30$, and ≥ 30) between the subjects of the present study

Table 1. Characteristics of subjects

	Males	Females	*t* value	*p* value
No of subjects	549	708		
Age (years)	16.5 (0.9)	16.7 (0.9)	−3.47	0.0005
Height (cm)	170.5 (5.9)	158.4 (5.2)	38.4	<0.0001
Weight (kg)	61.6 (10.4)	51.5 (7.0)	20.5	<0.0001
Waist circumference (cm)	72.7 (8.1)	71.2 (6.2)	3.95	<0.0001
Body mass index	21.2 (3.2)	20.5 (2.5)	4.05	<0.0001
Systolic blood pressure (mmHg)	117 (10)	106 (9)	18.7	<0.0001
Diastolic blood pressure (mmHg)	63 (9)	61 (9)	2.95	0.003
Triglyceride (mg/dL)	52 (50-55)	51 (50-54)	0.31	0.76
HDL-cholesterol (mg/dL)	60 (12)	66 (14)	−8.82	<0.0001
Fasting blood glucose (mg/dL)	88 (7)	86 (6)	5.31	<0.0001
Fasting blood insulin (μIU/mL)	5.8 (5.6-6.1)	6.5 (6.2-6.8)	−3.36	0.0008
HOMA-IR	1.26 (1.20-1.32)	1.37 (1.31-1.43)	−2.55	0.01
HOMA-β	89 (85-93)	106 (103-111)	−4.70	<0.0001
Adiponectin (μg/mL)	10.6 (4.1)	12.0 (4.6)	−5.67	<0.0001
Leptin (ng/mL)	1.5 (1.4-1.6)	6.1 (5.8-6.4)	−37.8	<0.0001
High sensitive-CRP (ng/mL)	154 (139-169)	107 (99-116)	5.83	<0.0001
Ghrelin (fmol/mL)	45 (43-49)	49 (46-53)	−1.40	0.16

Data are expressed as the mean, with the standard deviation in parentheses. Because of the high skewness in distribution, the values for triglyceride, fasting blood insulin, HOMA-IR, HOMA-β, leptin, high sensitive-CRP and ghrelin were obtained by antilog transformation of the arithmetic mean of log-transformed values. These data are expressed as the mean, with the 95% confidence interval in parentheses. Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, homeostasis assessment of insulin resistance: HOMA-β, HOMA-derived β-cell function.

and the general adolescent population in 2006-2008[14]. The 90th values of waist circumference (≥80 cm and ≥79 cm, for males and females, respectively), systolic (≥129 mmHg and ≥119 mmHg, respectively) and diastolic (≥75 mmHg and ≥73 mmHg, respectively) blood pressure, triglyceride (≥106 mg/dL and ≥95 mg/dL, respectively), FBG (≥96 mg/dL and ≥93 mg/dL, respectively), HOMA-IR (≥2.59 and ≥2.68, respectively) and the 10th percentile value of HDL-cholesterol (<46 mg/dL and <50 mg/dL, respectively) were used as cut-offs for the present study.

Statistical Analyses

Highly skewed variables in distribution were log transformed to raise unimodal symmetry, which is indicated by Ln( ) hereafter to highlight the transformation. Gender differences were detected by unpaired Student's *t*-test. Subjects were divided into four groups as follows: 0, 1, 2, and ≥3 CV risk factors for each gender. Tukey's multiple comparison was carried out for differences between any two groups with a trend test using contrast. To assess the impact on the levels of HOMA-IR, HOMA-β, or FBG, simple regression analysis was performed using the levels of the other CV risk factors as dependent variables and the levels of HOMA-IR, HOMA-β, or FBG as independent variables. To determine whether leptin levels were associated with the presence or absence and with the number of CV risk factors after adjustment for waist circumference or body mass index, another multivariate regression analysis was carried out using the Ln(leptin) levels as the dependent variable and waist circumference, BMI, and the presence of CV risks or the number of CV risk factors. Statistical analysis was performed with PASW® Statistics 18 software (SPSS Inc., Tokyo, Japan). $P<0.05$ was considered significant.

Results

Male adolescents had higher mean values of waist circumference, blood pressure, and FBG than females, while females had a higher HDL-cholesterol level than males (**Table 1**). Gender differences were present in the mean values of Ln(leptin), adiponectin, and Ln(hs-CRP).

The number of adolescents who had 0, 1, 2, 3, 4, and 5 risk factors was 306, 166, 52, 23, 2, and 0 subjects in males, and 413, 218, 58, 17, 2, and 0 subjects

Table 2. Frequent combinations of the cardiovascular risks in subjects with 2 risks

	Hypertension	Raised TG	Decreased HDL-C	Hyperglycemia
Males				
Abdominal obesity	7	3	5	4
Hypertension		8	2	8
Raised TG			8	4
Decreased HDL-C				3
Females				
Abdominal obesity	3	3	8	4
Hypertension		3	3	13
Raised TG			13	4
Decreased HDL-C				4

Abbreviations; TG, triglyceride: HDL-C, HDL-cholesterol.

in females, respectively. Among the subjects with 2 CV risk factors, frequent combinations of CV risks were hypertension and hyperglycemia, raised triglyceride and decreased HDL-cholesterol levels in both genders, and hypertension and raised triglyceride levels in males (**Table 2**).

We then divided the male and female subjects into four groups as follows: 0, 1, 2, and ≥3 CV risk factors. *P* values for the trend of all five CV risk factors and Ln(HOMA-IR) were $p<0.0001$ in both males and females (**Fig. 1**). Multiple comparison analysis showed that the mean values of all five CV risk factors and Ln(HOMA-IR) levels significantly worsened in both genders when adolescents had one CV risk factor (**Fig. 1**). Among the biomarkers, *p* values for the trend of Ln(leptin), adiponectin, Ln(hs-CRP), and Ln(ghrelin) were <0.0001, <0.0001, <0.0001, and 0.003 in males and <0.0001, 0.0006, 0.0002, and 0.23 in females, respectively (**Fig. 2**). Multiple comparison analysis showed that the mean values of Ln(leptin) in males, and those of Ln(leptin) and adiponectin in females significantly worsened when adolescents had one CV risk factor (**Fig. 2**).

We determined the impact of having any one of the CV risk factors on other CV risk factor levels (**Table 3**). The presence of any one of the CV risk factors was associated with another one or more CV risk factors, except for hyperglycemia in males. In particular, abdominal obesity was associated with significantly worsening levels of triglyceride, HDL-cholesterol, and insulin resistance in males, and HDL-cholesterol and insulin resistance in females. The effect of HOMA-IR and FBG levels on the other CV risk factors was determined in males because of no association between the presence of hyperglycemia and the levels of remaining CV risk factors. Regression analysis revealed that levels of Ln(HOMA-IR) were strongly associated with the levels of abdominal obesity ($t=8.83$, $p<0.0001$), systolic blood pressure ($t=3.09$, $p=0.002$), Ln(triglyceride) ($t=12.04$, $p<0.0001$), and HDL-cholesterol (-6.82, $p<0.0001$) and that Ln(HOMA-β) was also strongly associated with the levels of abdominal obesity ($t=8.11$, $p<0.0001$), systolic blood pressure ($t=2.47$, $p=0.01$), Ln(triglyceride) ($t=10.37$, $p<0.0001$), and HDL-cholesterol (-6.18, $p<0.0001$), while FBG levels were not significantly associated with other CV risk factors, except for Ln(triglyceride) levels ($t=2.50$, $p=0.01$).

Abdominal obesity was also associated with the worsening of all four biomarkers in males, and leptin and adiponectin levels in females. Ln(leptin) levels were associated with the number of CV risk factors in both genders and with the presence of any CV risks in males after adjustment for waist circumference or BMI (**Table 4**).

Discussion

The present study showed that the levels of all CV risk factors and HOMA-IR significantly and simultaneously worsened when adolescents had one of the CV risk factors in both genders. Having one CV risk factor indicated the worsening of other CV risk factor levels in adolescents. In particular, the development of abdominal obesity had a harmful effect on the levels of other CV risk factors and biomarkers.

Attitudes and physical morbidities that develop during adolescence are thought to have a profound effect on long-term health[13], suggesting that maintaining a healthy condition with no CV risks until adolescence decreases the prevalence of CV diseases in adulthood; however, little is known about the associa-

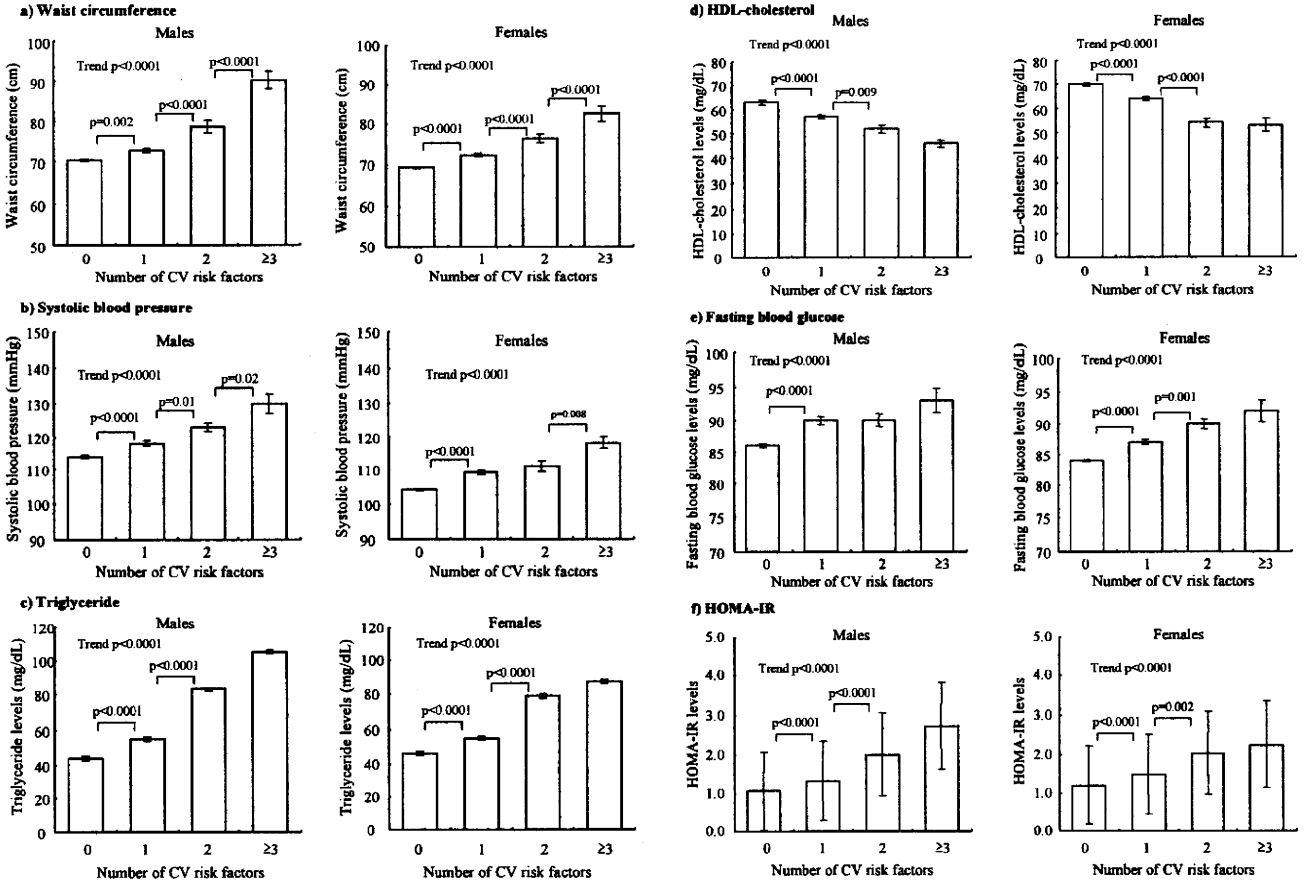

Fig. 1. Association between the total number of cardiovascular risk factors and the waist circumference (a), systolic blood pressure (b), triglyceride (c), HDL-cholesterol (d), fasting blood glucose (e), and HOMA-IR (f). Each bar shows the mean and the standard error of the mean. Because of the high skewness in distribution, the mean values for triglyceride and HOMA-IR were obtained by antilog transformation of the arithmetic mean of log-transformed values. Statistical analysis was carried out by Tukey's multiple comparison, and *p* values are shown when the value was significant between any two successive groups.

tion between having one CV risk factor and the levels of other CV risk factors in the general adolescent population. Another problem in the pediatric field is that there have been few long-term longitudinal studies from children to the middle-aged or even the elderly. Many pediatric investigators have used the 90th percentile values for cutoffs of CV risk factors in children and adolescents[13]. The criteria of the International Diabetes Federation also recommend using the 90th percentile value of waist circumference to diagnose abdominal obesity for children aged 6 to < 16 years of age. We thesefore determined the 90th percentile values for CV risk factors based on the data of the present study and used them as the cutoffs for CV risk factors. The present study showed that having one of the CV risk factors was associated with worsening levels of all CV risk factors and HOMA-IR. The data indicate that it is important to determine the presence or absence of these CV risk factors before and/or during adolescence, ant that primary prevention of all CV risk factors is needed for the general adolescent population.

Development of abdominal obesity had a harmful effect on the levels of other CV risk factors and biomarkers in the present study. Large, community-based studies in adults have shown that abdominal visceral adipose tissue is strongly associated with adverse metabolic risk profiles in the general population[16, 17]. These previous findings and the present data show that the development of abdominal obesity is a key factor among the CV risk factors for the accumulation of metabolic risk profiles, not only in adults but also in the dolescent general population.

A CV risk factor accompanies a clustering of

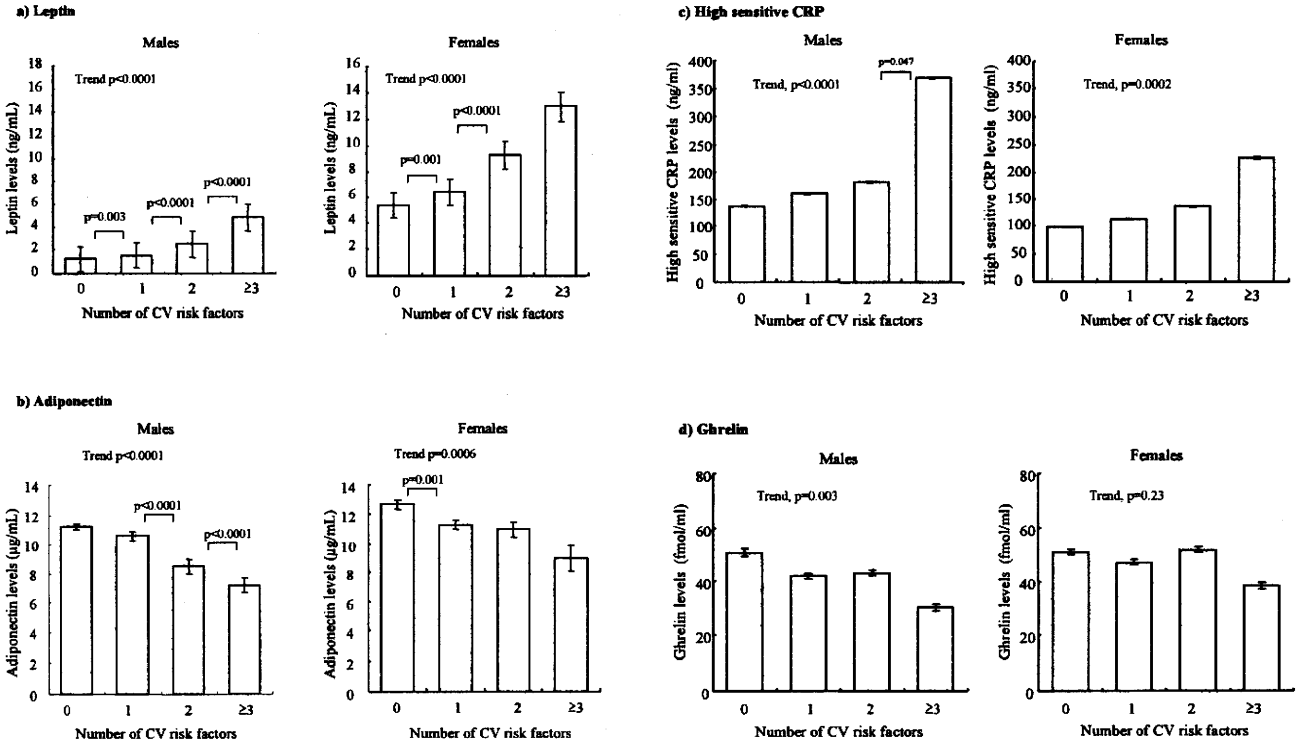

Fig. 2. Association between the total number of cardiovascular risk factors and the levels of leptin (a) and adiponectin (b), high sensitive-CRP (c) and desacyl-ghrelin (d). Each bar shows the mean and the standard error of the mean. Because of the high skewness in distribution, the mean values for leptin, high sensitive CRP, and desacyl-ghrelin were obtained by antilog transformation of the arithmetic mean of log-transformed values. Statistical analysis was carried out by Tukey's multiple comparison, and p values are shown when the value was significant between any two successive groups.

other CV risk factors, including abdominal obesity, impaired glucose tolerance, hypertension, and dyslipidemia, which have been collectively termed metabolic syndrome in both children and adults. In subjects with 2 CV risk factors, frequent combinations of CV risks were hypertension and hyperglycemia or raised triglyceride and decreased HDL-cholesterol levels in both genders. These combinations are well known in adult population[18, 19]. The present study showed that these combinations started as early as in adolescencs.

Among the CV risk factors, hyperglycemia in males was not associated with any other CV risk factors in the present study. Hyperglycemia is known to be associated with a clustering of CV risk factors in adolescents in several areas[20, 21], suggesting the presence of ethnic and/or gender differences. We found that a surrogate marker of insulin resistance is a candidate for one of the CV risk factors because levels of HOMA-IR were strongly associated with levels of other CV risk factors in male adolescents. Abe *et al.* also showed that insulin levels, but not levels of FBG, were associated with the number of CV risk factors in obese boys with a mean age of 12 years[22]. In the male Japanese pediatric and adolescent population, levels of fasting insulin and/or HOMA-IR, but not FBG, might be useful parameters for one of the CV risk factors, which is consistent with previous studies[22, 23].

Beta-cell function in adolescent males was associated with the levels of other CV risk factors in the present study. In contrast with the steady decline in β-cell function with age observed in adults[24, 25], increasing insulin resistance in children and adolescent could be well compensated by an increase in β-cell function, as measured with HOMA-β, to maintain glucose homeostatis[26], as was shown in previous studies[26, 27].

Of the biomarkers examined in the present study, only leptin levels significantly increased with an increase in the number of CV risk factors in both genders (**Fig. 2**). Ln(leptin) levels were associated with the presence or number of CV risk factors after adjustment for waist circumference or BMI (**Table 4**). A previous report showed that leptin levels were the most sensitive marker for predicting the accumulation

Table 3. Comparison of subjects with no cardiovascular risk factors with those with one cardiovascular risk factor

	No CV Risk factor	Abdominal obesity	High SBP	High DBP	Raised TG	Low HDL-C	High FBG	High HOMA-IR*
Males								
No of subjects	306	22	30	40	21	22	42	17
Waist (cm)	70.3 (4.4)	87.5 (7.0)[a]	72.5 (4.8)[d]	69.4 (4.3)	70.3 (4.8)	71.0 (4.7)	69.6 (4.6)	71.6 (5.4)
SBP (mmHg)	114 (8)	116 (7)	132 (4)[a]	124 (8)[a]	111 (6)[d]	110 (8)[d]	115 (8)	114 (8)
DBP (mmHg)	61 (8)	59 (9)	70 (9)[a]	79 (4)[a]	60 (8)[d]	56 (8)[d]	63 (7)	61 (6)
TG (mg/dL)	44 (42-47)	55 (45-66)[d]	48 (42-56)	46 (40-52)	122 (115-129)	55 (47-65)[d]	46 (41-52)	54 (48-61)[d]
HDL-C (mg/dL)	63 (11)	56 (5)[c]	63 (13)	64 (12)	55 (8)[b]	41 (4)[a]	61 (10)	61 (11)
FBG (mg/dL)	86 (6)	87 (5)	86 (6)	85 (6)	88 (6)	86 (5)	99 (3)[a]	96 (5)[b]
Insulin (μIU/mL)	5.0 (4.7-5.3)	9.0 (7.6-10.8)[a]	5.7 (4.6-7.0)	4.4 (3.6-5.4)	7.6 (6.4-9.0)[b]	5.7 (4.9-6.6)	6.1 (5.3-7.1)[d]	12.7 (11.9-13.7)[a]
HOMA-IR	1.1 (1.0-1.1)	1.9 (1.6-2.3)[a]	1.2 (1.0-1.5)	0.9 (0.7-1.2)	1.6 (1.4-2.0)[b]	1.2 (1.0-1.4)	1.5 (1.3-1.7)[a]	3.0 (2.9-3.2)[a]
Leptin (ng/mL)	1.2 (1.2-1.3)	4.5 (3.5-5.9)[a]	1.3 (1.1-1.5)	1.4 (1.1-1.7)	1.7 (1.3-2.1)[d]	1.1 (0.8-1.3)	1.2 (1.0-1.4)	2.2 (1.6-2.9)[a]
AN (μg/mL)	11.2 (3.9)	8.9 (3.6)[c]	11.1 (2.6)	12.1 (4.4)	9.5 (3.6)	9.1 (3.9)[d]	11.2 (5.5)	10.8 (5.2)
hs-CRP (ng/mL)	136 (121-153)	368 (210-645)[a]	127 (90-180)	167 (110-253)	122 (84-176)	122 (61-244)	134 (95-193)	130 (82-206)
Ghrelin (fmol/mL)	51 (47-55)	29 (21-39)[b]	34 (24-48)[b]	45 (33-62)	47 (33-67)	47 (32-69)	45 (36-56)	49 (35-68)
Females								
No of subjects	413	34	45	56	30	35	42	32
Waist (cm)	69.3 (4.4)	82.8 (3.8)[a]	71.4.(4.7)[c]	70.1 (4.4)	70.0 (4.8)	70.3 (4.0)	70.9 (4.5)[d]	72.2 (3.9)[b]
SBP (mmHg)	104 (7)	106 (8)	123 (6)[a]	117 (9)[a]	106 (6)	101 (6)[d]	104 (8)	103 (8)
DBP (mmHg)	60 (7)	60 (8)	72 (8)[a]	77 (3)[a]	59 (7)	56 (9)[d]	60 (7)	58 (8)
TG (mg/dL)	46 (44-48)	52 (47-57)	41 (36-46)	43 (39-47)	114 (107-121)[a]	62 (56-68)[a]	53 (46-60)[d]	60 (54-67)[a]
HDL-C (mg/dL)	70 (12)	63 (9)[c]	72 (12)	72 (13)	61 (8)[b]	45 (5)[a]	68 (14)	63 (10)[c]
FBG (mg/dL)	84 (5)	85 (4)	86 (4)[d]	85 (4)	87 (4)[c]	85 (4)	96 (3)[a]	92 (6)[a]
Insulin (μIU/mL)	5.9 (5.6-6.2)	7.6 (6.5-9.0)[c]	5.9 (5.2-6.8)	5.6 (4.8-6.5)	8.8 (7.6-10.2)[a]	6.9 (5.7-8.3)	8.0 (6.3-10.0)[b]	15.3 (14.1-16.5)[a]
HOMA-IR	1.2 (1.1-1.3)	1.6 (1.4-1.9)[c]	1.3 (1.1-1.4)	1.2 (1.0-1.4)	1.9 (1.6-2.2)[a]	1.4 (1.2-1.7)	1.9 (1.5-2.4)[a]	3.4 (3.2-3.8)[a]
Leptin (ng/mL)	5.4 (5.1-5.7)	10.5 (8.6-13.0)[a]	5.0 (4.2-6.1)	5.1 (4.4-5.9)	7.1 (5.7-9.0)[c]	6.5 (5.4-7.9)[d]	6.3 (5.3-7.4)	7.8 (6.3-9.7)[a]
AN (μg/mL)	12.7 (4.5)	10.7 (4.0)[d]	11.7 (5.0)	11.9 (4.6)	10.5 (5.7)[d]	9.7 (3.7)[b]	12.0 (4.8)	11.1 (4.3)
hs-CRP (ng/mL)	98 (89-107)	135 (94-194)	116 (84-160)	88 (71-110)	105 (77-143)	130 (87-196)	117 (78-177)	149 (87-256)[d]
Ghrelin (fmol/mL)	51 (47-55)	47 (34-67)	56 (43-73)	42 (32-54)	36 (26-49)[d]	62 (47-82)	45 (34-59)	43 (32-60)

Data are expressed as the mean, with the standard deviation in parentheses. Because of the high skewness in distribution, the values for triglyceride, fasting blood insulin, HOMA-IR, leptin, high sensitive-CRP and ghrelin were obtained by antilog transformation of the arithmetic mean of log-transformed values. These data are expressed as the mean, with the 95% confidence interval in parentheses. Statistical analysis was carried out between subjects with no cardiovascular risk factors and those with one cardiovascular risk factor: a, $p<0.0001$; b, $p<0.001$; c, $p<0.01$; d, $p<0.05$.
*; Eight male and 12 female subjects with high HOMA-IR levels had high FBG levels, but did not have any other CV risk factors.
Abbreviations: AN, adiponectin; DBP, diastolic blood pressure; CV, cardiovascular; FBG, fasting blood glucose; HDL-C, High-density lipoprotein-cholesterol; HOMA-IR, homeostasis assessment of insulin resistance; hs-CRP, high sensitive C-reactive protein; SBP, systolic blood pressure; TG, triglyceride.

Table 4. Impact of presence or number of the CV risk factors, waist circumference, and body mass index on the levels of log-transformed leptin levels by multivariate regression analysis

	Presence of CV risks*		Number of CV risks		Waist		Body mass index	
	t value	*p* vlaue	*t* value	*p* value	*t* value	*p* value	*t* value	*p* value
Males	2.45	0.01			8.24	<0.0001	0.93	0.35
			2.99	0.003	7.59	<0.0001	0.99	0.32
Females	1.63	0.10			7.97	<0.0001	4.26	<0.0001
			2.46	0.01	7.61	<0.0001	4.18	<0.0001

*; Presence or absence of any cardiovascular (CV) risk factors.

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of CV risk factors in the general population of elementary school children[28]. Nakatani *et al.* reported that serum leptin was a more useful biomarker of metabolic abnormalities than high-molecular-weight adiponectin in general male adolescents[23]. These previous and the present data suggest that leptin levels are a candidate for predicting the presence and/or accumulation of CV risk factors in the general pediatric population.

A limitation of the present study is that the adolescent subjects voluntarily participated in the project. Heavier adolescents were less inclined to volunteer; however, this means that the results obtained from the present study can be applied to the general adolescent population. The second limitation is that we defined the CV risk factors on the basis of gender- and Japanese-specific 90th percentile values (10th percentile for HDL-cholesterol), but not on the basis of universally used criteria, such as the International Diabetes Federation criteria[29] or the American Heart Association/the National Heart, Lung, and Blood Institute criteria[30, 31]. One reason why we did not use universal criteria was that we did not intend to compare the prevalence of metabolic syndrome. The second reason was that the mean values of each CV risk factor are different among countries[32, 33], suggesting that the definition should be gender- and ethnic-specific to understand the pathophysiology of CV risk factors in each area.

Conclusion

The levels of CV risk factors and HOMA-IR significantly and simultaneously worsened when adolescents had one of the CV risk factors in both genders. It is important to determine the presence or absence of these CV risk factors during adolescence, because having one CV risk factor indicates the start of the accumulation of CV risk factors in the general adolescent population. Our data also suggest that further interventional studies are warranted to test the impact of the alleviation of any one of these CV risks, especially abdominal obesity, on the incidence of other CV risks in the adolescent population.

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EDITORIAL

Correction of the QT Interval in Children

Naokata Sumitomo, MD, PhD

Introduction and Genetic Topics of Long QT Syndrome (LQTS)

LQTS is characterized as prolonged ventricular repolarization with a high incidence of sudden cardiac death because of ventricular arrhythmias, such as torsades de pointes or ventricular fibrillation. Recent advances in genetic studies have revealed 12 genetic abnormalities on the locus of the chromosomes in chromosome 3, 4, 7, 11, 12, 17, 20 and 21.[1] These genetic abnormalities result in decreased function of the potassium channels, increased or prolonged function of calcium channels, or increased function of the sodium channels, which are responsible for the prolongation of ventricular repolarization and consequently cause prolongation of the QT interval.

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Recently, not only genetic mutations, but also the segment of the genetic mutation has been reported as important for revealing the risk of cardiac events in some types of LQTS. In LQT1, those with transmembrane mutations of KCNQJ are at a higher risk of cardiac events than those with C-terminal mutations,[2,3] and in LQT2, those with pore site mutations of KCNH2 are reported to be at a higher arrhythmic risk than those with non-pore site mutations.[4,5] According to the location of the genetic mutation, the patients with dominant-negative ion current mutations have a longer QTc interval and higher risk of cardiac events than those with haploinsufficiency mutations associated with LQT1.[2] These functional analyses of ion channels may clarify the severity and prognosis of some cases of LQTS in the near future.

In addition to QTc prolongation associated with transmembrane mutations in LQT1[3] and LQT2[5] patients, the $QT_{peak-end}$ ($QT_{end}-QT_{peak}$) interval is also prolonged in these patients (**Figure**). The $T_{peak-end}$ is thought to reflect the transmural dispersion of the ventricular repolarization, and the longer the $T_{peak-end}$ is, the greater the chance that a possible cardiovascular accident may occur. In LQT1 patients with transmembrane mutations, the $T_{peak-end}$ is prolonged more by sympathetic nerve stimulation than in patients with C-terminal mutations[3] (**Figure A**), which may explain the high occurrence of cardiovascular events during exercise in patients with transmembrane mutations.

Diagnosis of LQTS

Unlike the recent advances in genetic testing and functional analysis of ion channels, the clinical diagnosis of LQTS is mainly based on resting 12-lead ECG, clinical symptoms and family history.[6] In children, a total LQTS score <4 points has been reported as associated with an absence of cardiac events in the future, if the children have no cardiac events in their past history.[7] In pediatric patients with a history of cardiac events, family history of cardiac events, lower medication compliance, and lower age at diagnosis are significant risk factors for a cardiac event in the future.[7]

It is well known that the corrected QT interval using Bazett's formula[8] ($QTc=QT/RR^{1/2}$) is not suitable for use in children whose heart rates are faster than 75 beats/min. Fridericia's formula ($QTc=QT/RR^{1/3}$) is more suitable than Bazett's for correction of the QT interval for lower and also higher heart rates,[9] but it has not become the standard method for the correction of the QT interval. One reason may be that the power calculation ($RR^{1/3}$) cannot be done with a standard electronic calculator, but requires a computer or functional electronic calculator. Some ECG machines in Japan can calculate both Bazett's correction and Fridericia's correction and by using such machines, more data can be made be available for the correction of the QT interval in children.

Although the criteria of Schwartz et al[6] using Bazett's formula have been highly useful, they mention nothing about age, faster heart rates, or neonates, infants and children. QTc measurements using Bazett's formula have been reported as useful for screening for LQTS in neonates and infants,[10,11] but those studies did not use Fridericia's formula, so it is not possible to determine the efficacy of the latter formula in infants.

Prevalence of LQTS in Children

Schwartz et al[10] reported on the prevalence of LQTS in 44,596 neonates by recording their ECGs. The number of patients with QTc >450 ms was 177 infants (0.41%), 28 had a QTc between 451 and 460 ms (0.06%), 14 had a QTc between 461 and 470 ms (0.03%), and 31 had a QTc >470 ms (0.07%). Genetic mutations were found in 12 of the 28 (43%) with a QTc >470 ms and in 4 of the 14 (29%) with a QTc between 461 and 470 ms. The authors concluded that the prevalence of definite LQTS was at least 1:2,534 (0.04%) apparently healthy live births.[10] Another previous report on the prevalence of LQTS stated it was 0.02% in the normal population,[12] and 0.038% in normal children.[13]

In this issue of the Journal, Hazeki et al[14] found a discontinuous distribution of the QTc interval in the upper 0.025 percentile of school children by using Fridericia's formula. The prevalence of this discontinuous distribution was 4 in

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Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan
Mailing address: Naokata Sumitomo, MD, PhD, Department of Pediatrics and Child Health, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan. E-mail: naokata@med.nihon-u.ac.jp
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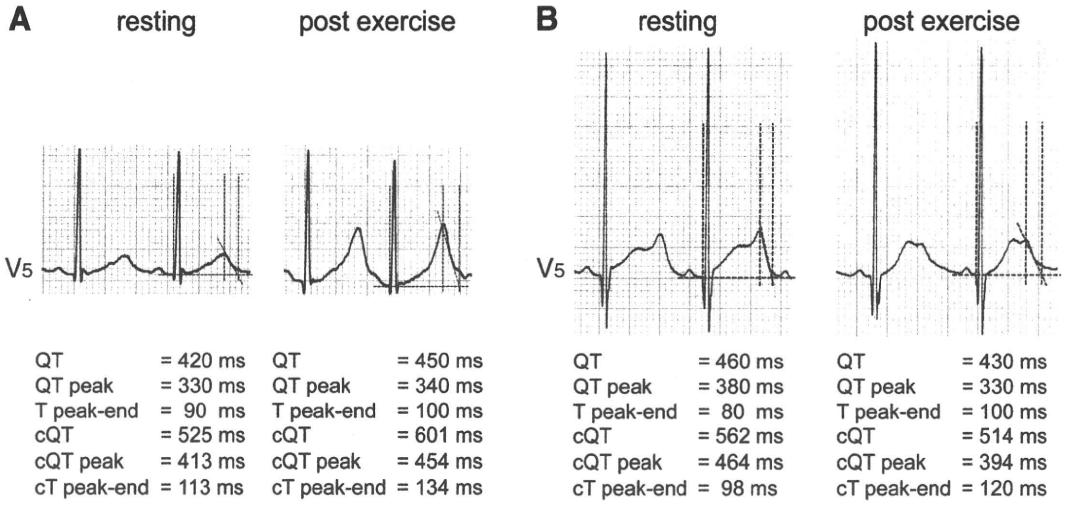

Figure. Change in the ECG during a treadmill exercise test in a patient with Romano-Ward syndrome: resting ECG and the ECG at 2 min after the maximal treadmill exercise test in 2 patients with confirmed genetic long QT syndrome. The prolongation of the cQT and cT peak-end differed in the LQT1 and LQT2 patients. (**A**) The resting and post exercise ECGs in the LQT1 patient. The cQT and cT peak-end were prolonged after the exercise in the LQT1 patient. (**B**) The resting and post exercise ECGs in the LQT2 patient. The cT peak-end was prolonged; however, the cQT shortened after the exercise in the LQT2 patient. QT, QT interval; QT peak, interval between the onset of the QRS and peak of the T wave; T peak-end, interval between the peak of the T wave and end of the T wave; cQT, corrected QT interval using Bazett's formula; cQT peak, corrected QT peak interval using Bazett's formula; cT peak-end, corrected T peak-end interval using Bazett's formula.

4,655 subjects (0.086%). The same group reported an identical prevalence using Bazett's formula[15] in the same subjects. However, their prevalence of LQTS in the normal population was more than in the other reports. They did not perform a genetic study, and they intended to screen for all possible LQTS patients with their cut-off value.

There has been no previous standard cut-off for screening school children using Fridericia's formula. Hazeki et al[14] propose a tentative cut-off QTc value of 430 ms for 1st graders, 445 ms for 7th graders, and 440 and 455 ms for 10th grade males and females, respectively. Further investigation with a genetic study and determination of abnormal QTc values using Fridericia's formula are needed.

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CASE REPORT

**Naokata Sumitomo · Takahiro Nakamura · Junji Fukuhara
Toshiko Nakai · Ichiro Watanabe · Hideo Mugishima
Masayasu Hiraoka**

Clinical effectiveness of pulmonary vein isolation for arrhythmic events in a patient with catecholaminergic polymorphic ventricular tachycardia

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Abstract An 18-year-old woman with catecholaminergic polymorphic ventricular tachycardia (CPVT) underwent pulmonary vein isolation (PVI) because of frequent and inappropriate shocks from an implantable cardioverter defibrillator (ICD) associated with atrial fibrillation (AF) with a rapid ventricular response. While the PVI did not completely suppress the AF induced by an isoproterenol infusion, the Holter monitor recordings demonstrated a major decrease in the clinical episodes of AF and ventricular tachyarrhythmias in association with a reduced high-frequency (HF) component and ratio of the low-frequency (LF) component power to the HF component (LF/HF) after the PVI. The PVI can decrease the substrates that trigger and maintain the AF when it involves a pulmonary vein origin, and may exert an additional effect on the sympathetic nerve input to the heart. The PVI may be an adjunctive therapy for CPVT cases with drug refractory AF causing inappropriate ICD discharges.

Key words Catecholaminergic polymorphic ventricular tachycardia · Pulmonary vein isolation · Catheter ablation · Atrial fibrillation · Heart rate variability

Introduction

Pulmonary vein isolation (PVI) is widely performed for the treatment of atrial fibrillation (AF),[1–4] but its effectiveness in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) who show a frequent association of this arrhythmia is limited.[5] Here we report the clinical effectiveness of PVI in controlling not only AF episodes but also inappropriate discharges of implantable cardioverter defibrillators (ICDs) due to a rapid ventricular response.

N. Sumitomo (✉) · T. Nakamura · J. Fukuhara · H. Mugishima
Department of Pediatrics and Child Health, Nihon University School of Medicine, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan
Tel. +81-3-3972-8111 (ext. 2442); Fax +81-3-3957-6186
e-mail: naokata@med.nihon-u.ac.jp

T. Nakai · I. Watanabe
Department of Cardiology, Nihon University School of Medicine, Tokyo, Japan

M. Hiraoka
Department of Cardiovascular Diseases, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

Case report

An 18-year old woman underwent catheter ablation for PVI because of inappropriate shocks from an ICD due to AF with a rapid ventricular response. She had had her first experience of convulsions at 16 months old and was treated for epilepsy in another hospital. She first fainted at 10 years old while she was running in school, followed by several more episodes of exercise-induced syncope. She was referred to our hospital for the evaluation of a syncopal attack while riding a bicycle when she was 11 years old. There was no history of any unexpected deaths or syncope among her family members.

The patient was admitted to our hospital and diagnosed with CPVT because of the induction of sustained bidirectional ventricular tachycardia (VT) but no AF during exercise and an infusion of isoproterenol. The echocardiogram was normal. Repeat treadmill tests were performed, and propranolol was found to be partially effective in preventing the CPVT. While stellate ganglionectomy or ICD implantation was considered as an alternate therapeutic option, the latter was selected to prevent her from sudden cardiac death and due to incomplete effectiveness of β-blocker treatment to exercise-induced VT. Because there was no documentation of any atrial arrhythmias at or before the time of implantation and the size of a dual chamber ICD might have been a little bit too large for her, she was implanted with a single chamber ICD for the prevention of sudden cardiac death when she was 11 years old. She was discharged from the hospital and then followed up at the outpatient clinic with 1 mg/kg of propranolol, the dose of propranolol was then gradually increased to 2 mg/kg, and

120 mg of verapamil was then added. However, her follow-up Holter monitor recording and treadmill exercise test revealed partial suppression of VT episodes initially but later recurrences of VT. Clinically she continued to experience presyncopal episodes without fainting, and these episodes were shown to be either due to severe bradycardia without VT in certain occasions, and therefore the propranolol was changed to 75 mg of atenolol when she was 17 years old. A genetic analysis revealed a missense mutation of *RyR2* (A7420G).

The follow-up records from the ICD interrogation demonstrated several shocks had been repeatedly delivered to rapid ventricular rhythms and with varying RR intervals without restoring sinus rhythm (Fig. 1). Holter monitoring revealed frequent AF episodes converting to frequent premature ventricular contractions (PVCs) and bidirectional VT, and then VT to AF. These sequences of arrhythmic events were repeatedly recorded (Fig. 2A).

The patient was admitted once again to our hospital for the control of her episodes of AF. Since she had taken three kinds of antiarrhythmic agents without prevention of AF episodes and resultant inappropriate ICD discharges, PVI was chosen as a therapeutic option for her because of its effectiveness in the treatment of this arrhythmia.[1-4] Although left stellate ganglionectomy might have been another option in her case, this procedure was not chosen because of her clinical symptoms being resistant to high doses of β-blockers. After written informed consent was obtained, she underwent catheter ablation for AF. Each pulmonary vein was isolated individually, then complete block between the pulmonary vein potentials and atrial activity was confirmed. Despite the successful PVI, AF as well as bidirectional VT was still inducible with an infusion of 0.04 μg/kg of isoproterenol per minute. After the PVI, her clinical symptoms greatly improved without any palpitations or syncope, and she had no signs of inappropriate ICD shocks. The Holter monitor demonstrated a major decrease in the episodes of AF and PVCs, as well as VT, while she continued to take the same dose of medication as before the PVI (Fig. 2B).

A frequency domain analysis of the 24-h heart rate variability using Holter records demonstrated a transient

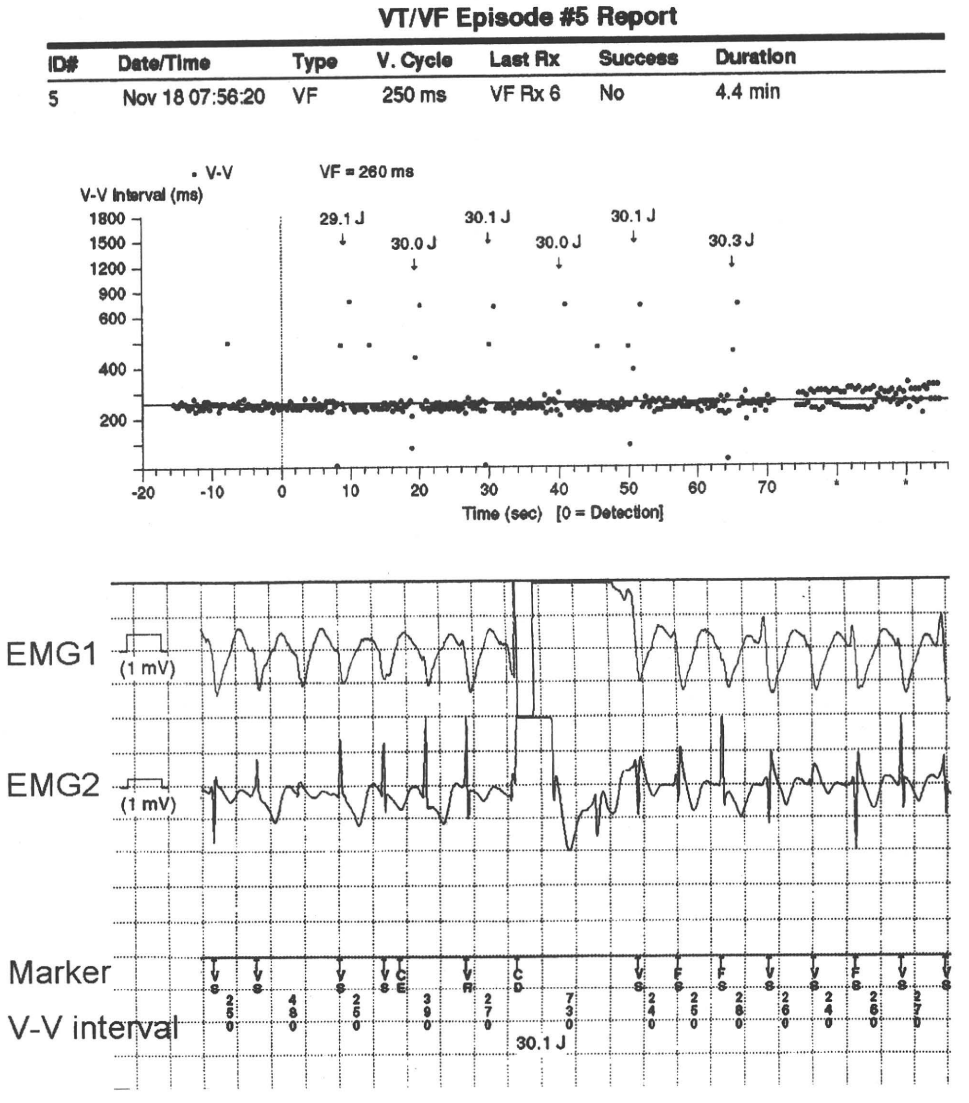

Fig. 1. Internal recordings from an implantable cardioverter defibrillator (ICD) showing inappropriate shocks due to atrial fibrillation (AF) with a rapid ventricular response. **Upper panel** Six episodes of inappropriate shock deliveries due to AF. **Lower panel** Intracardiac electrocardiograms from an ICD. Note the RR interval changed beat by beat. *EGM1*, can to coil lead electrocardiogram; *EGM2*, ventricular tip to ventricular ring electrocardiogram

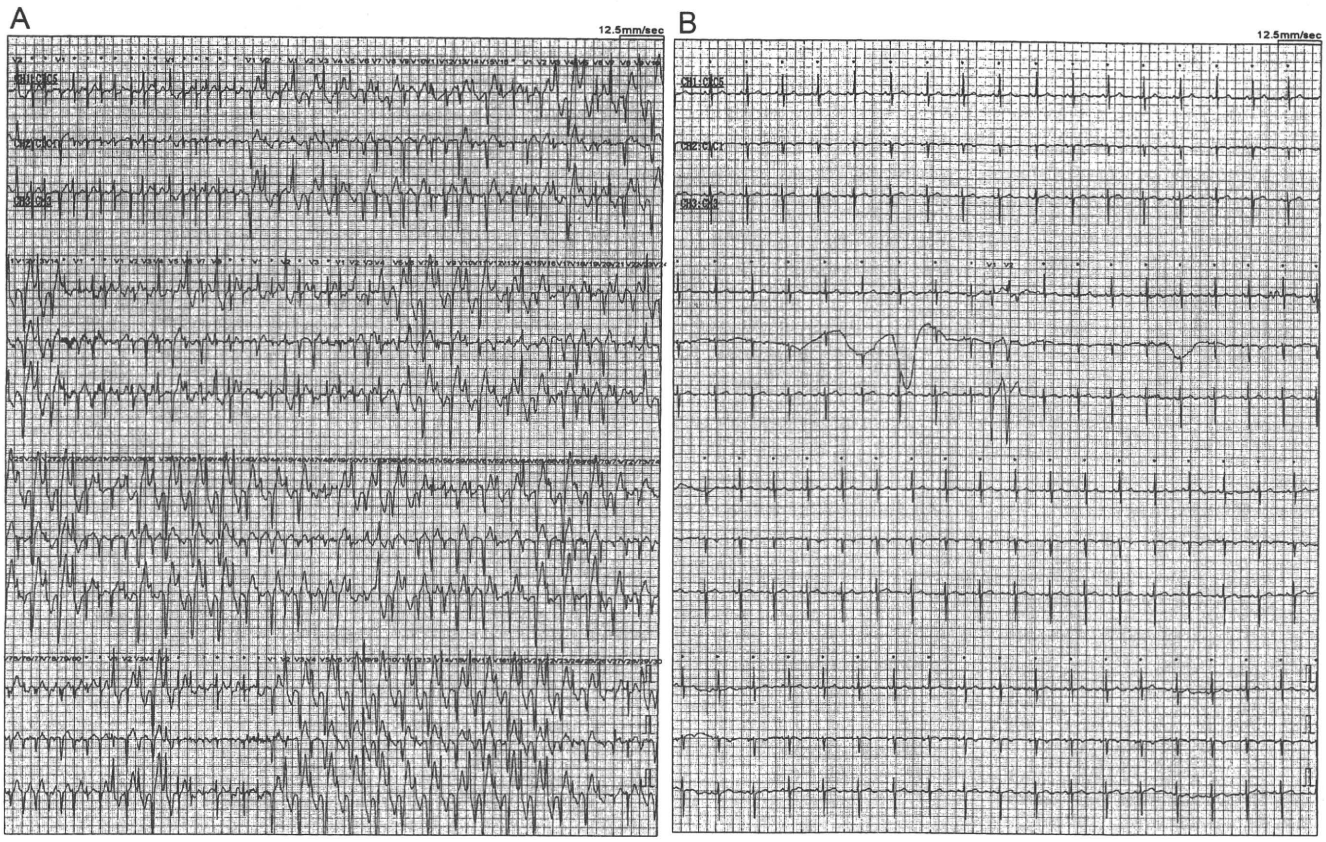

Fig. 2A,B. Holter electrocardiography records before and after pulmonary vein isolation (PVI). **A** Daytime Holter recordings when the patient was walking before the PVI, while she was taking 75 mg of atenolol. Note that the atrial fibrillation changed to a bidirectional VT and then the AF reappeared. **B** Daytime Holter recording when the patient was walking after the PVI, while the patient was taking the same dose of atenolol. There were no AF episodes, and only one ventricular couplet was detected during this 24-h recording

decrease in the high-frequency (HF) component and a marked decrease in the ratio of the low-frequency (LF) component power to the HF component (LF/HF) after the PVI (Fig. 3). She was since followed up for 11 months, without any evidence of ICD discharges.

Discussion

This report demonstrated that PVI could prevent the frequent attacks of AF and resultant inappropriate shocks from an ICD due to a rapid ventricular response, and suppress tachycardia-induced VT that were refractory to the conventional medical treatment, although PVI itself could not achieve a complete elimination of the arrhythmia substrate in the patient with CPVT.

The treatment strategy for CPVT that is generally recommended is a high dose of β–blockers,[6,7] verapamil,[8] and flecainide,[9] and an ICD implantation. However, the implantation of ICDs may not always prevent a dismal outcome.[10,11] Further, patients with CPVT are frequently associated with supraventricular arrhythmias including AF,[12,13] and may suffer from inappropriate ICD discharges due to a rapid ventricular response, which could be a fatal event.[11] Therefore, special caution must be paid to suppress AF with rapid ventricular responses in CPVT patients with ICD implantation. Also, recently PVI was reported to be effective in controlling an atrial tachycardia in a patient with CPVT.[5] Consequently, we attempted to control the AF by performing PVI in a case with AF episodes associated with frequent inappropriate ICD discharges. We chose PVI, since the patient's AF episodes were resistant to full doses of β-blockers plus verapamil. Flecainide was not tested for her due to lack of data being available as to its effectiveness at the time of ICD implantation.

Although a complete dissociation between the pulmonary vein potentials and left atrial activity was achieved in our case, AF and VT were still inducible by an isoproterenol infusion. The apparently conflicting results after PVI in this case indicated that despite the complete elimination of the pulmonary vein activity acting as the triggering mechanisms for the AF, arrhythmic substrates in the atria and ventricle inherent to CPVT were still preserved. Surprisingly, the spontaneous episodes of AF, PVCs, and VT markedly decreased after the PVI as compared to that before the procedure, and her clinical symptoms much improved. The sequence of events in this patient after PVI could be interpreted in the following way. Pulmonary vein foci could have been a triggering mechanism for provoking rapid and irreg-

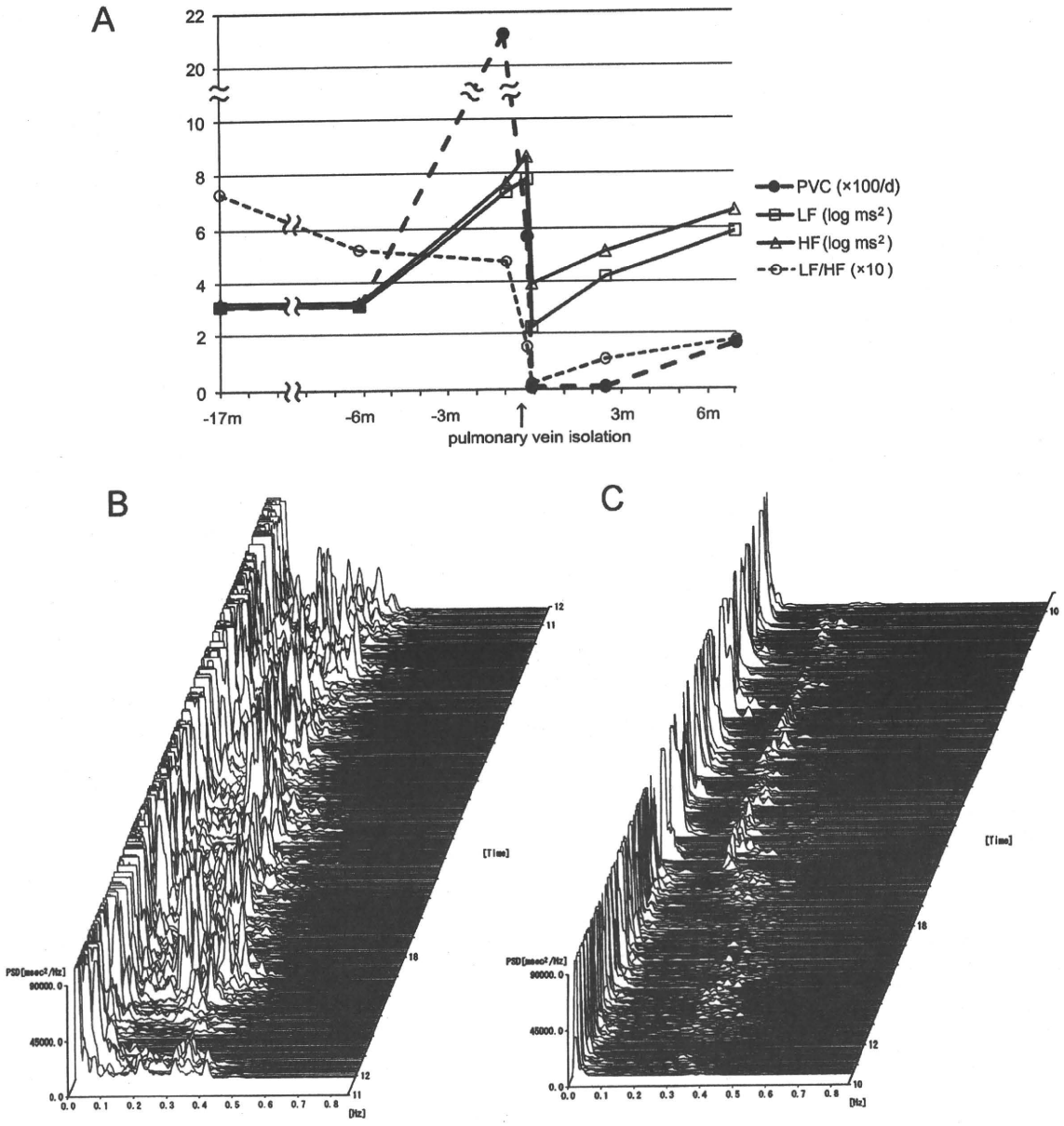

Fig. 3A–C. Changes in the parameters for the heart rate variability and incidence of premature ventricular contractions. **A** Changes in the number of premature ventricular contractions and parameters for the heart rate variability before and after the PVI. **B** Three-dimensional fast Fourier transform (FFT) analysis of the 24-h Holter recording before the PVI. Note that a marked prominence of the high-frequency (HF) and low-frequency (LF) powers were recorded throughout the day. **C** Three-dimensional FFT analysis after the PVI. The HF and LF powers became markedly diminished. *PVC*, premature ventricular contraction; *LF*, low-frequency power of the heart rate variability analysis; *HF*, high-frequency power of the heart rate variability analysis; *LF/HF*, low frequency/high frequency power ratio

ular excitations of the atria which may have led to AF, which, in turn, may have caused a rapid ventricular response and inappropriate ICD shocks. Further, AF that provokes inappropriate ICD shocks could potentially be fatal in these patients because it may provoke a catecholamine release from the sympathetic nerve terminals in the heart which, in turn, induced reappearance of AF, PVCs, and VT in CPVT.[11] This type of vicious cycle was somewhat prevented by the PVI eliminating the triggering and possible maintenance effects of pulmonary vein foci on AF episodes, which was a possible basis of the reduced incidence of AF leading to the elimination of the rapid ventricular response, inappropriate ICD discharges, and tachycardia-induced VT.

Another possibility for the reduced incidence of AF and VT after the PVI may be related to the sympathetic denervation as a result of the PVI. Left stellate ganglionectomy was reported to be effective for QT shortening and heart rate changes in long QT syndrome.[14] Recent reports have demonstrated that sympathetic denervation decreased the incidence of VT by reducing the input for the internal release of catecholamines from the heart in patients with CPVT.[15] However, there have been no reports showing that