A   B

Ligand-binding domain

Coactivator complexes

PPARγ ligand

PPARγ   RXR

Corepressor complexes   HDAC

PPARγ   RXR

DNA-binding domain

PPRE   PPRE

Fig 1. Transactivation and active repression. PPARγ functions as a heterodimer with RXR. (A) In the presence of ligand, PPARγ binds to coactivator complexes, resulting in the activation of target genes. (B) In the absence of ligand, PPARγ binds to the promoters of several target genes and associates with corepressor complexes, leading to active repression of target genes. HDAC, histone deacetylase; PPAR, peroxisome proliferator-activated receptor; PPRE, PPAR responsive element; RXR, retinoid X receptor.

(NCoR) and silencing mediator of retinoid and thyroid hormone receptors, histone deacetylases (HDACs) and transducin β-like protein 1 (TBL1). HDACs are essential in maintaining repressed chromatin structure and TBL1 exchanges a corepressor complex for a coactivator complex in the presence of ligand![2]

Many nuclear receptors are proposed to sequester inflammatory transcription factors, such as nuclear factor-κB (NF-κB) and AP-1, by inhibiting their DNA-binding activities, resulting in inhibition of inflammatory target genes. In the presence of ligand, PPARγ also interacts with inflammatory transcription factors and inhibits their DNA-binding activities. PPARγ blocks clearance of the corepressor complex in a ligand-dependent manner, and PPARγ stabilizes the corepressor complex bound to the promoter of inflammatory genes![3] It was demonstrated that PPARγ associates with the protein inhibitor of activated STAT1 (PIAS1), which is a small ubiquitin-like modifier (SUMO)-E3 ligase, in a ligand-dependent manner. PIAS1-induced SUMOylation of the ligand-binding domain of PPARγ enables the receptor to maintain NCoR on the promoter of inflammatory genes![4] These are the suggested mechanisms of PPARγ transrepression.

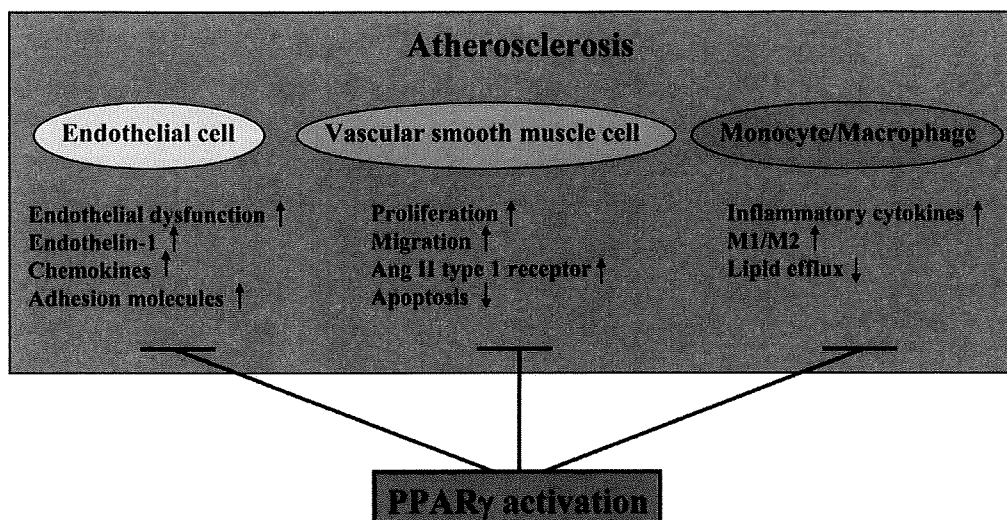## PPARγ Ligands

Natural and synthetic ligands bind to PPARγ, resulting in conformational change and activation of PPARγ. The PGD2 metabolite, 15d-PGJ2, was the first endogenous ligand for PPARγ to be discovered. Although 15d-PGJ2 is the most potent natural ligand of PPARγ, the extent to which its effects are mediated through PPARγ in vivo remains to be determined. Two components of oxidized low density lipoprotein (ox-LDL), the 9-hydroxy and 13-hydroxy octadecadienoic acids (HODE), are also potent endogenous activators of PPARγ![15,16] Activation of 12/15-lipoxygenase induced by interleukin (IL)-4 also produced endogenous ligands for PPARγ;[17] however, whether these natural ligands act as physiological PPARγ ligands in vivo remains unknown. The antidiabetic thiazolidinediones (TZDs), such as troglitazone, pioglitazone, ciglitazone and rosiglitazone, which are used to control glucose concentration in patients with diabetes mellitus (DM), are pharmacological ligands of PPARγ. They bind PPARγ with various affinities and it is conceiv-

able that their insulin-sensitizing and hypoglycemic effects are exerted by activating PPARγ. However, the molecular mechanisms by which TZDs affect insulin resistance and glucose homeostasis are not fully understood. They seem to mediate their effects primarily through adipose tissue, because TZDs alter the expression level of genes that are involved in lipid uptake, lipid metabolism and insulin action in adipocytes. TZDs enhance adipocyte insulin signaling and reduce the release of free fatty acids. TZDs also decrease the inflammation of adipose tissue that is induced by obesity and contributes to increased insulin resistance. There is a possibility that TZDs improve insulin sensitivity in skeletal muscle and liver, the main insulin-sensitive organs, through these multiple adipocentric actions. PPARγ has been demonstrated to have an antiinflammatory effect, leading to initiation of treatment trials for patients with inflammatory diseases. RXR, which interacts with the PPARs, is activated by 9-cis retinoic acid. When combined as a PPAR:RXR heterodimer, the PPAR ligands and 9-cis retinoic acid act synergistically on PPAR responses.

PPARγ and Atherosclerosis

Atherosclerosis is a complex process to which many different factors contribute. Injury of the endothelium, proliferation of VSMCs, migration of monocytes/macrophages, and the regulatory network of growth factors and cytokines are important in the development of atherosclerosis. In addition, chronic inflammation of the vascular wall is also involved. As mentioned earlier, PPARγ has antiinflammatory effect. PPARγ ligands have been shown to reduce production of inflammatory cytokines, such as IL-1β, IL-6, inducible nitric oxide synthase and tumor necrosis factor-α (TNF-α), by inhibiting the activity of transcription factors such as activator protein-1 (AP-1), signal transducers and activators of transcription (STAT), and NF-κB in monocytes/macrophages[2,3] Those findings suggest that PPARγ activation may have beneficial effects in modulating inflammatory responses in atherosclerosis. Interestingly, expression of PPARγ has been demonstrated in atherosclerotic plaques[8] Macrophages affect the vulnerability of plaque to rupture and they are implicated in the secretion of matrix metalloproteinases (MMPs), enzymes that are important in the degradation of extracellular matrix. In macrophages and VSMCs, PPARγ

Atherosclerosis

| Endothelial cell | Vascular smooth muscle cell | Monocyte/Macrophage |

Endothelial dysfunction ↑
Endothelin-1 ↑
Chemokines ↑
Adhesion molecules ↑

Proliferation ↑
Migration ↑
Ang II type 1 receptor ↑
Apoptosis ↓

Inflammatory cytokines ↑
M1/M2 ↑
Lipid efflux ↓

PPARγ activation

Fig 2. In atherosclerosis, PPARγ inhibits progression of the atherosclerotic lesion. PPAR, peroxisome proliferator-activated receptor.

ligands have been shown to reduce the expression of MMP-9, resulting in the inhibition of migration of VSMCs, and plaque destabilization.[3,4] Although activation of T lymphocytes represents a critical step in atherosclerosis, PPARγ ligands also reduce the activation T lymphocytes.[8] Recently, it was reported that PPARγ is a key regulator of M1/M2 polarization.[9] Classically activated macrophages (M1) express a high level of pro-inflammatory cytokines and reactive oxygen species, whereas alternatively activated macrophages (M2) play an antiinflammatory role in atherosclerosis. PPARγ agonists prime monocytes into M2 and PPARγ expression is enhanced by M2 differentiation.[20]

VSMC proliferation and migration are also critical events in atherosclerosis and vascular-intervention-induced restenosis. TZDs inhibit both these changes in the VSMCs and neointimal thickening after vascular injury.[21–24] Furthermore, TZDs induce apoptosis of VSMCs via p53 and Gadd45.[25,26] Angiotensin II (AngII) plays an important role in vascular remodeling via the AngII type 1 receptor (AT₁R) and accelerates atherosclerosis. Although AngII induces transcriptional suppression of PPARγ, activation of PPARγ inhibits AT₁R gene expression at a transcriptional level in VSMCs.[27–29] Expression of adhesion molecule by ECs, leading to adhesion of leukocytes, is a critical early step in atherosclerosis. PPARγ ligands inhibit the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 and decreased production of chemokines, such as IL-8 and monocyte chemotactic protein-1 (MCP-1) via suppressions of AP-1 and NF-κB activities in ECs.[30–32] PPARγ ligands also inhibit MCP-1-induced monocytes migration.[33] Endothelin-1 (ET-1) is involved in the regulation of vascular tone and endothelial functions, and induces proliferation of VSMCs. In bovine aortic ECs, PPARγ ligands suppressed transcription of the ET-1 promoter by interfering with AP-1.[34]

PPARγ activation by major oxidized lipid components of ox-LDL, 9-HODE and 13-HODE has an important role in the development of lipid-accumulating macrophages through transcriptional induction of CD36, a scavenger receptor.[35] These findings suggest that atherogenic ox-LDL particles could induce their own uptake through activation of PPARγ and expression of CD36, leading to atherosclerosis. How-

ever, several studies have demonstrated that activation of PPARγ does not promote lipid accumulation in either mouse or human macrophages.[36–38] Liver X receptor α (LXRα) is an oxysterol receptor that promotes cholesterol excretion and efflux by modulating expression of ATP-binding cassette transporter 1 (ABCA1).[37,38] LXRα was recently identified as a direct target of PPARγ in mouse and human macrophages.[39,40] Although the PPARγ-induced increase in CD36 expression might accelerate lipid uptake in macrophages, subsequent activation of LXRα and upregulation of ABCA1 appear to induce lipid efflux.

Diep et al have demonstrated that rosiglitazone and pioglitazone attenuate the development of hypertension and structural abnormalities, and improve endothelial dysfunction in AngII-infused rats.[41] These TZDs also prevented upregulation of AT₁R, cell cycle proteins, and inflammatory mediators. Rosiglitazone, but not the PPARα ligand fenofibrate, prevented hypertension and endothelial dysfunction in DOCA-salt hypertensive rats.[42] It has been reported that serum levels of the soluble CD40 ligand are elevated in acute coronary syndrome and associated with increased cardiovascular risk. Treatment with rosiglitazone decreased the serum levels of soluble CD40 and MMP-9 in type 2 diabetic patients with coronary artery disease.[43] Taking all the evidence together, PPARγ ligands may prevent the progression of atherosclerotic lesions, particularly in patients with DM (Fig 2).

PPARγ and Ischemic Heart Disease

As the effects of PPARγ on the heart are not fully understood, we and others have examined whether PPARγ is involved in various heart diseases. Although the expression of PPARγ in cardiac myocytes is low compared with adipocytes, PPARγ ligands seem to act on cardiac myocytes.[7,44] We demonstrated that PPARγ ligands inhibited the cardiac expression of TNF-α at the transcriptional level, in part by antagonizing NF-κB activity.[7] Because TNF-α expression is elevated in the failing heart and has a negative inotropic effect on cardiac myocytes, treatment with PPARγ ligands may prevent the development of congestive heart failure. Diabetic cardiomyopathy, which is characterized by
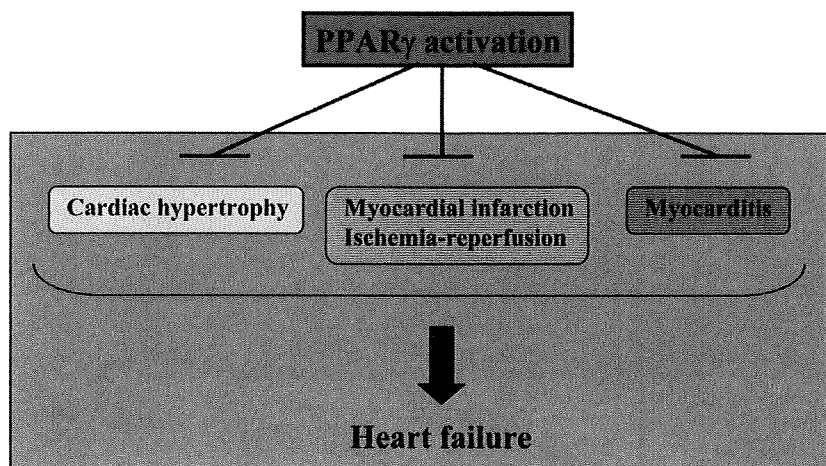
Fig 3. Actions of PPARγ in heart diseases. PPARγ inhibits the progression of heart failure following cardiac hypertrophy, myocardial infarction, ischemia-reperfusion injury, and myocarditis. PPAR, peroxisome proliferator-activated receptor.

systolic and diastolic dysfunction, is a major complication of DM, and therefore TZDs seem to be beneficial for the impaired cardiac function in patients with DM. Following our study, the role of PPARγ in myocardial ischemia-reperfusion (IR) injury has been elucidated[45-48] In animal models, PPARγ ligands reduced the size of the myocardial infarct and improved contractile dysfunction after IR through inhibition of the inflammatory response. IR injury activates JNK, and subsequently JNK induces increases in both AP-1 DNA-binding activity and apoptotic cells. It has been shown in rats that rosiglitazone inhibits the activation of JNK and AP-1 after myocardial IR[46] Furthermore, pioglitazone has been reported to attenuate left ventricular remodeling and heart failure after myocardial infarction (MI) in mice[49] Both of these effects of TZDs ligands were associated with decreases in inflammatory cytokines and chemokines[49,50]

PPARγ and Cardiac Hypertrophy

The PPARγ ligands, troglitazone, pioglitazone and rosiglitazone, inhibited AngII-induced hypertrophy of neonatal rat cardiac myocytes[51-53] Because generalized PPARγ gene deletion causes embryonic lethality, we examined the role of PPARγ in the development of cardiac hypertrophy in vivo using heterozygous PPARγ-deficient (PPARγ$^{+/-}$) mice[53] Pressure overload-induced cardiac hypertrophy was more prominent in heterozygous PPARγ$^{+/-}$ mice than in wild-type (WT) mice. Treatment with pioglitazone strongly inhibited the pressure overload-induced cardiac hypertrophy in WT mice and moderately in PPARγ$^{+/-}$ mice[53] Thereafter, 2 other groups examined the role of PPARγ in the heart by using cardiomyocyte-specific PPARγ knockout mice[54,55] Duan et al reported that these mice develop cardiac hypertrophy through elevated NF-κB activity[54] and unexpectedly, rosiglitazone induced cardiac hypertrophy in both the WT mice and cardiomyocyte-specific PPARγ knockout mice through activation of p38 MAP kinase independent of PPARγ. Ding et al reported that cardiomyocyte-specific PPARγ knockout mice displayed cardiac hypertrophy from approximately 3 months of age and then progress to dilated cardiomyopathy;[55] most mice died from heart failure within 1 year after birth. Mitochondrial oxidative damage and reduced expression of manganese superoxide dismutase were recognized in the cardiomyocyte-specific PPARγ knockout mice[55] These mice models demonstrate that PPARγ is essential for protecting cardiomyocytes from

stress and oxidative damage, although the expression level of PPARγ in cardiomyocytes is low. On the other hand, Son et al demonstrated that cardiomyocyte-specific PPARγ transgenic mice develop dilated cardiomyopathy associated with increased uptake of both fatty acid and glucose[56] Rosiglitazone increased this glucolipotoxicity in cardiomyocyte-specific PPARγ transgenic mice. If PPARγ in the heart is expressed at a high level, rosiglitazone may cause cardiotoxic effects; however, as noted earlier the expression level of PPARγ in the heart is quite low.

PPARγ and Myocarditis

Experimental autoimmune myocarditis (EAM) is a T-cell-mediated disease characterized by infiltration of T cells and macrophages, leading to massive myocarditis necrosis, which develops into heart failure in the chronic phase[57] The onset of EAM in rats occurs approximately 2 weeks after the first immunization with porcine cardiac myosin. At this time, small numbers of CD4$^+$ T cells and macrophages start to infiltrate into the myocardium and various cytokines are expressed. Macrophage inflammatory protein-1α (MIP-1α) is a C-C chemokine that induces leukocyte accumulation in tissue sites of inflammation. We previously demonstrated that MIP-1α mRNA and protein are highly expressed in the hearts of rats with EAM from day 11 after first immunization[57] Th1 cells produce interferon-γ (IFN-γ), which is mainly involved in cell-mediated immune responses, whereas Th2 cells produce IL-4, IL-5, IL-6, IL-10 and IL-13, which participate in humoral responses. Immune dysfunction associated with autoimmune disease is known to involve an imbalance between Th1 and Th2 cells.

It has been reported that pioglitazone treatment markedly reduces the severity of myocarditis in a rat model of EAM[58,59] Pioglitazone suppressed expression of inflammatory cytokines and activation of myocardiogenic T cells in the myocardium of EAM rats[58] The mRNA levels of MIP-1γ were upregulated in the hearts of EAM rats, but not in the hearts of those in the pioglitazone group. Furthermore, treatment with pioglitazone decreased the expression levels of pro-inflamatory cytokine (TNF-α and IL-1β) genes and Th1 cytokine (IFN-γ) genes, and increased the expression levels of Th2 cytokine (IL-4) gene[59] These results suggest that PPARγ ligands may have beneficial effects on myocarditis by inhibiting MIP-1α expression and modulating the Th1/Th2 balance (**Fig 3**).

Efficacy and Safety of TZD Treatment in the Clinical Setting

Despite the beneficial effects of TZDs in the basic experiments, their propensity to cause fluid retention is a serious side-effect. Clinical studies report TZD-induced peripheral fluid retention, and an increase in plasma volume in 2–5% of patients on monotherapy[60] Fluid retention was more likely to occur with concomitant insulin use, and in patients with underlying cardiac dysfunction or renal insufficiency. The exact mechanisms for TZD-induced fluid retention are not well understood, and it remains unclear whether TZDs directly cause the development of de novo congestive heart failure. It is known that the level of vascular endothelial growth factor is increased in the patients who develop fluid retention with TZD therapy[61] and this may lead to peripheral edema through increased vascular permeability. The insulin-sensitizing action of TZDs also induces water and salt retention. PPARγ is highly expressed in the kidney and collecting-duct-specific PPARγ knockout mice demonstrated no effects of TZD on fluid retention or the expression level of sodium channel ENaC-γ[62,63] These findings suggest that activation of the sodium channel in the collecting duct cells expressing PPARγ may be a mechanism of fluid retention. In patients without evidence of heart failure, careful examination did not reveal any worsening of left ventricular function by TZDs[64] There are very few studies investigating the safety of TZDs in patients with preexisting heart failure. Although a recent study demonstrated that there is not a direct association between the risk of fluid retention and the baseline degree of severity of heart failure in diabetic patients treated with TZDs, the prescription of TZDs for patients with established heart failure should be avoided at present[60,65]

The PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study has shown that pioglitazone significantly decreases the occurrence of all-cause mortality, nonfatal MI, and nonfatal stroke in patients with type 2 DM and macrovascular diseases[66] Pioglitazone significantly reduced the occurrence of fatal and nonfatal MI by 28% in the PROactive study[66] Although there was a 1.6% absolute increase in heart failure hospitalizations in the pioglitazone group compared with the placebo group, the number of heart-failure-related deaths was almost identical. In contrast to the PROactive study, it has been recently reported that rosiglitazone treatment is associated with increased incidence of MI by meta-analysis[67,68] Although meta-analysis has a number of limitations and the increased risk in MI is still controversial, those results attracted the attention of many clinicians. There are some differences in the actions of pioglitazone and rosiglitazone. Pioglitazone has more beneficial effects on the lipid profile than rosiglitazone[69] As mentioned earlier, rosiglitazone, but not pioglitazone, induced cardiac hypertrophy by a non-PPARγ-mediated pathway[54] Pioglitazone represses NF-κB activation and VCAM-1 expression in a PPARα-dependent manner[70] Pioglitazone was recently reported to increase the number and function of endothelial progenitor cells (EPCs) in patients with stable coronary artery disease and normal glucose tolerance[71] Pioglitazone may induce angiogenesis by modulating EPC mobilization and function. In the future, more mechanistic studies are required to investigate the differences in action between pioglitazone and rosiglitazone.

Conclusions

The American Heart Association (AHA) and American Diabetes Association (ADA) have released a consensus statement that advises caution regarding the use of TZDs in patients with known or suspected heart failure[72] Because there is a possibility that TZDs may unmask asymptomatic cardiac dysfunction by increasing plasma volume, they should be avoided in patients with congestive heart failure of New York Heart Association (NYHA) class III or IV. The data from in vitro studies suggest that TZDs exert direct actions on vascular cells and cardiomyocytes, independent of their glucose-mediated mechanisms. Further studies using tissue-specific gene targeting mice are necessary to address in vivo the pleiotropic effects of PPARγ on the cardiovascular system. If the beneficial roles of PPARγ can be solved, modulation of PPARγ may become a promising therapeutic strategy for cardiovascular diseases. Because cardiac hypertrophy can be seen even in normotensive diabetic patients, and diabetic cardiomyopathy is a major complication of DM, antidiabetic agents such as the TZDs would be expected to have beneficial effects on cardiac hypertrophy and dysfunction in patients with DM. It has been already clarified that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, statins, have pleiotropic effects in cardiovascular diseases. The effects of PPARγ ligands are similar to those of statins in many respects. A recent study demonstrated that statins activate PPARγ through ERK and p38 MAP-kinase-dependent cyclooxygenase-2 expression in macrophages[73] Further studies are needed to elucidate the molecular mechanisms of the pleiotropic effects of PPARγ ligands in cardiovascular disease.

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原　著

Pitavastatin improves cardiac function of patients with ischemic heart failure

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Abstract

Background : Pitavastatin is a HMG-CoA reductase inhibitor (statin) with pleiotropic effects, and improves the prognosis of patients with congestive heart failure (CHF) and may also be effective against coronary artery disease (CAD).

Methods and results : We enrolled 38 CHF patients who had previously abnormal lipid metabolism and had been prescribed pitavastatin 2 mg for over 1 year. We analyzed brain natriuretic peptide (BNP) and left ventricular ejection fraction (LVEF) between the ischemic heart failure complications (CAD(+) group) and the control group (CAD(-) group). The serum levels of HDL cholesterol (HDL-C) concentration significantly increased in the both groups after treatment. There were no significant differences in the lipid profile comparing the two groups. The plasma BNP levels decreased in the both groups, and the BNP level in the CAD (+) group showed a tendency for decrease compared with the CAD(-) group after 12 months (-82 [-410, 145] vs. -43 [-306, 180]). The CAD(+) group showed a tendency for the increase in LVEF greatly compared with the CAD(-) group (7.0 [2.0, 44.9] vs. 2.8 [-38.9, 35.5]) after 12 months.

Conclusion : Pitavastatin administration decreased the BNP level and increased LVEF in both groups, especially in the CAD(+) group.

Key words : HMG-CoA reductase inhibitors, heart failure, brain natriuretic peptide, left ventricular ejection fraction

Introduction

Heart failure is the terminal form of cardiovascular disease that may occur as the result of many etiologies, and though various methods of treatment have been suggested, mortality and morbidity are still high[1]. Heart failure worsens patients' quality of life, and can lead to poor prognosis. Prevalence increases with age, and reaches 10% for those over 75 years old.

Mortality rate from heart failure is also increasing, despite the fact that the overall mortality rates from cardiovascular diseases remain stable. The key in heart failure treatment is early detection and treatment to retard its progression.

In a recent study, Sano et al determined that the p53 gene was involved in the pathogenesis of heart failure[2]. Ventricular hypertrophy was induced in a model mouse by increasing heart pressure via aortic

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banding. In this study, hypoxia-inducible factor-1 (Hif-1) first increased, then as a result lead to an increase of vascular endothelial growth factor (VEGF), thereby induced neo-angiogenesis, and inhibited auxocardia progressing into a heart failure. The tumor suppressor gene p53 is known to suppress Hif-1, and in cases where p53 gene had been activated, heart failure was induced twice as fast than the control group. Despite auxocardia, heart failure did not occur for those that had p53 inactivated.

A report recently published also indicates that HMG-CoA reductase inhibitors (statins) have cardioprotective characteristics, thereby improving the prognosis of patients with heart failure[3]. Statins inhibit synthesis of cholesterol within the liver, and activate LDL receptors to decrease blood cholesterol levels. Also, primary and secondary prevention of cardiovascular events has been confirmed in large scale clinical trials[4]. In addition, recent studies suggested that statins possess pleiotropic effects, such as auxocardia suppression, improvement of left ventricular diastolic function, and anti-inflammatory and anti-oxidation effects[5-7] which may prevent heart failure.

Pitavastatin (Livalo tablet ; manufactured by Kowa Company, Ltd., distributed through Kowa Pharmaceutical Co. Ltd.) is a statin clinically proven to have potent total cholesterol (TC), LDL cholesterol (LDL-C), and triglyceride (TG) level reduction, as well as to increase HDL cholesterol (HDL-C). Kibayashi et al report pitavastatin reduces the level of CRP via the MAPKs (mitogen-activated protein kinases) pathway. In addition, an anti-inflammatory effect, induced by significantly suppressing interleukin-8 production that is derived from CRP, has also been reported[8,9]. Another report indicates that pitavastatin, administered to experimental dogs with heart failure induced by high-frequency pacing, improved left ventricular diastolic function without affecting cardiac contractility[10]. According to the report, the eNOS expression increased at the mRNA level, and oxidative stress and vascular endothelial function improved as a result of pitavastatin administration. Another report also indicates that pitavastatin may also be effective against coronary artery disease (CAD), especially against

ischemia-reperfusion[11]. In addition, Tounai et al report pitavastatin suppressed p53 within nerve cells[12]. Hence pitavastatin may be effective in suppressing the onset and progression of heart failure.

CAD is a common cause for congestive heart failure in advanced countries[13]. In such cases, onset of tumor suppressor gene p53 and apoptosis are known to be enhanced within the coronary artery plaque[14]. In addition, in the apoptosis of ischemia-reperfusion that occurs after percutaneous coronary intervention (PCI), a common treatment of acute coronary syndrome (ACS), p53 onset is reported to be enhanced along with tumor necrosis factor-α (TNF-α), interleukin-6, and monocyte chemo-attractant protein-1 (MCP-1), and reports indicate that suppression of such factors may afford cardioprotection[15].

The key role of p53 in heart failure by CAD is currently being investigated. Pitavastatin is thought to improve heart failure through a mechanism such as suppression of p53, but its exact mechanism in ischemic and non-ischemic heart failure remains unknown.

Hence, this study group examined whether pitavastatin improves cardiac function of ischemic heart disease patients compared to non-ischemic heart disease patients.

Pitavastatin was administered for 12 months to patients who had heart failure and abnormal lipid metabolism, and its effect on cardiac functions was examined. Ischemic heart failure, in which p53 is thought to be strongly correlated with its onset, was compared to other heart failure of other etiologies (valvular disorders, arrhythmias, etc.).

Methods

Thirty-eight patients who visited Department of Cardiology, Seirei Yokohama General Hospital from Aug to Sept 2007, who had New York Heart Association (NYHA) class II or III heart failure, and who had previously been prescribed pitavastatin 2 mg for over 1 year, and had abnormal lipid metabolism, were enrolled into the study. We retrospectively analyzed the data, separately analyzing 19 patients with ischemic

Table 1　Baseline patient characteristics

	Total	CAD(−)	CAD(+)
n	38	19	19
Age (years)	65 ± 12	68 ± 15	63 ± 9
Sex (% male)	64	60	72
Smoking habit (%)	25	15	35
Duration of CHF (years)	3.2 ± 1.5	4.1 ± 1.9	2.9 ± 1.2
Hypertension (%)	30	25	35
Diabetes mellitus (%)	20	15	25
Total cholesterol (mg/dL)	236 ± 32	231 ± 38	239 ± 41
LDL cholesterol (mg/dL)	139 ± 30	136 ± 38	144 ± 28
Triglycerides (mg/dL)	148 (78, 201)	140 (76, 192)	151 (81, 220)
Systolic BP (mmHg)	120 ± 20	118 ± 22	124 ± 18
Diastolic BP (mmHg)	76 ± 12	74 ± 10	78 ± 14
Heart rate (beat/min)	64 ± 10	60 ± 10	68 ± 12
Medication (%)			
ACEI/ARB	98 (58/40)	95 (54/41)	100 (62/38)
Diuretics	88	90	86
Digoxin	68	72	64
β-blocker	78	82	74

Values are mean ± SD or median (25th, 75th percentile). P values for all data between the 2 groups were not significant. CHF, congestive heart failure ; BP, blood pressure ; ACEI, angiotensin-converting enzyme inhibitors ; ARB, angiotensin II receptor blockers.

heart failure complications (CAD(+) group), and 19 patients in the control group (CAD(−) group) with complications of non-ischemic heart failure (valvular disorder, arrhythmia, etc.). Patient backgrounds such as age, sex, and co-morbidities, were considered.

Lipid parameters including blood TC, LDL-C, HDL-C, and TG, were monitored before and 6, and 12 months after pitavastatin administration. Heart failure related parameters such as plasma concentration of brain natriuretic peptide (BNP) and left ventricular ejection fraction (LVEF) were monitored before and 12 months after the administration. Plasma concentration of BNP was assayed using a chemiluminescent enzyme immunoassay (SRL, Tokyo, Japan). LVEF was estimated by M-mode and 2-dimensional echocardiography (Xario, Toshiba, Japan).

Participants' written informed consent and local institutional review board approvals were obtained before the study.

Statistical analysis : One-sample t-test was utilized to assess effectiveness before and after pitavastatin administration. In either method, values below 5% on 12 months were considered statistically significant, and readings were recorded as mean ± SD.

Results

Patient backgrounds for the 38 patients enrolled are shown in **Table 1**. There were no significant differences in age, sex, lipid profiles, hemodynamic parameters, LVEF (**Table 2**), or medications between the CAD(+) and CAD(−) groups.

After treatment, the serum levels of TC and LDL-C concentration significantly decreased in the both groups. The serum levels of HDL-C concentration significantly increased in the both groups after treatment. There were no significant differences in the lipid profile comparing the two groups (**Table 2**). The plasma BNP levels decreased in the both groups, and the BNP level in the CAD(+) group showed a tendency for decrease compared with the CAD(−) group after 12 months (−82 [−410, 145] vs. −43 [−306, 180]) (**Figure 1A**).

Cardiac function improved in both groups following treatment with pitavastatin. The LVDd and LVDs significantly decreased, and the LVEF significantly in-

Table 2   Serial changes of several variables in patients with CHF

	CAD(−) (n = 19)			CAD(+) (n = 19)		
	Baseline	6 m	12 m	Baseline	6 m	12 m
NYHA	2.2 ± 0.8	2.0 ± 0.6	2.0 ± 0.6	2.0 ± 0.6	1.8 ± 0.6	1.8 ± 0.6
SBP(mmHg)	118 ± 22	114 ± 20	112 ± 18	124 ± 18	118 ± 16	116 ± 18
DBP(mmHg)	74 ± 10	72 ± 12	74 ± 12	78 ± 14	76 ± 12	74 ± 10
HR(beat/min)	60 ± 10	64 ± 8	62 ± 10	68 ± 12	72 ± 10	74 ± 8
TC(mg/dL)	231 ± 38	178 ± 25*	182 ± 14*	239 ± 41	182 ± 41*	169 ± 32†
LDL−C(mg/dL)	136 ± 38	87 ± 12*	88 ± 9 *	144 ± 28	94 ± 17*	83 ± 12†
TG(mg/dL)	140(76, 192)	136(75, 160)	135(76, 163)	151(81, 220)	137(78, 199)	148(75, 186)
BNP(pg/mL)	112(60, 244)	80(30, 174)*	69(36, 145)*	122(90, 221)	98(40, 221)*	40(24, 180)*
LVDd(mm)	60.2(58.0, 70.4)	58.0(56.9, 68.2)*	57.4(55.6, 66.8)*	59.1(55.4, 69.1)	58.0(53.4, 66.2)*	56.2(53.4, 63.0)*
LVDs(mm)	55.5(48.2, 60.4)	53.3(46.9, 58.4)*	51.4(45.5, 56.8)*	53.6(47.4, 59.9)	49.8(45.8, 56.9)*	47.8(44.1, 55.2)*
LVEF(%)	40.6 ± 7.8	41.3 ± 7.2	43.0 ± 6.7*	40.5 ± 8.0	48.8 ± 9.6*	45.2 ± 11.7*

Values are mean ± SD or median (25th, 75th percentile). SBP, systolic blood pressure ; DBP, diastolic blood pressure ; HR, heart rate ; TC, total cholesterol ; LDL−C, LDL cholesterol ; TG, triglycerides.
   * : p<0.05 vs baseline, † : p< 0.01 vs baseline.
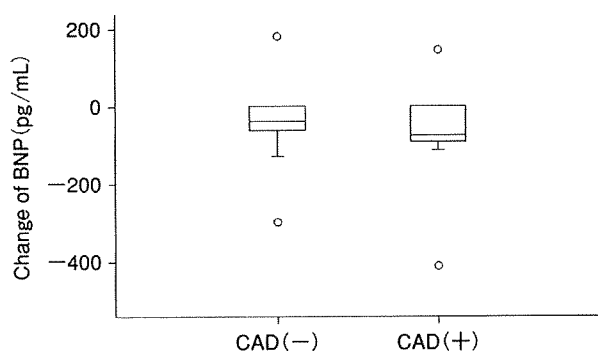
Figure 1A   Comparison of the changes in plasma level of BNP between CAD(−) group and CAD(+) group 12 months after treatment
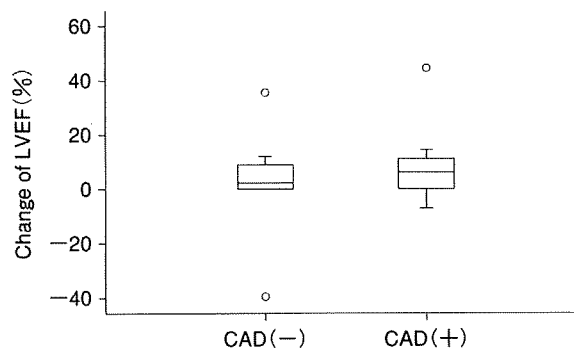
Figure 1B   Comparison of the changes in LVEF between CAD(−) group and CAD(+) group 12 months after treatment

creased in the both groups after treatment (**Figure 1 B**). The CAD(+) group showed a tendency for the increase in LVEF greatly compared with the CAD(−) group (7.0 [2.0, 44.9] vs. (2.8 [−38.9, 35.5]) after 12 months (**Figure 1B**). No major adverse events were observed.

Discussion

It has been reported that pitavastatin improved cardiac function in patients with heart failure[16]. In this study, we analyzed lipid profile and cardiac functional parameters between the ischemic heart failure complications (CAD(+) group) and the control group (CAD(−) group). Comparative analysis was conducted for each parameter before and after pitavasta-

tin administration. In this study, both TC and LDL−C levels experienced statistically significant improvements and HDL−C levels for the CAD(+) group increased after 12 months. The TG levels before administration were variable, and no statistically significant changes were observed in either group.

Pitavastatin administration decreased the BNP level and increased LVEF in both groups, especially in the CAD(+) group. BNP is a useful peptide marker in everyday clinical practice to monitor heart failure, as well as for diagnosis of cardiac disease and heart failure. BNP belongs to the natrium peptide (NP) family. The NP system, derived from the NP family, and NP receptors possess strong natriuretic and vasodilating properties, as well as strong suppressive effects on renin−angiotensin system and sympathetic nervous

system. BNP is primarily synthesized in the ventricle, and is released into the vasculature in response to excessive stretching of myocytes[17].

The authors suggested the reason BNP levels decreased and LVEF increased in both groups was similar to the *in vivo* findings of pitavastatin administration in experimental dog models with heart failure[9]. In the dog model, pitavastatin improved left ventricular diastolic function and vascular endothelial function. A recent study reported that pitavastatin therapy in angiotensin Ⅱ (Ang Ⅱ)-induced left ventricular hypertrophy improved diastolic dysfunction and attenuated cardiac fibrosis, cardiomyocyte hypertrophy, coronary perivascular fibrosis, and medial thickening[18]. Ang Ⅱ-induced oxidative stress, cardiac transforming growth factor (TGF) $\beta 1$ expression, and Smad 2/3 phosphorylation were all attenuated by pitavastatin. In this fashion, pitavastatin may improve LVEF through inhibition of the TGF-β-Smad 2/3 signaling pathway. Alternatively, rosuvastatin, a potent statin analog, is also reported to decrease hospitalization rate due to cardiac disease in elderly patients with heart failure, but to be ineffective in suppressing cardiovascular events[19]. Further prospective analysis is necessary.

Particularly, in the CAD (+) group, BNP level decreased whereas the LVEF level improved. BNP and p53 expression are reported to change dynamically under critical condition such as ACS[13, 14, 20], and perhaps under such conditions, agents such as pitavastatin, which suppresses p53, may provide higher treatment effects.

While only a hypothesis at present, as p53 is difficult to measure in actual clinical practice, pitavastatin holds the possibility of improving the prognosis of heart failure arising from ischemic cardiac disorders, as it improved BNP levels, which is a highly sensitive marker for sudden death after ischemic cardiac disorder, and which also reflects the prognosis of myocardial infarction.

In this study, pitavastatin administration for 12 months to patients with cardiac disorder who also suffered from a lipid metabolism abnormality was retrospectively analyzed. BNP level and LVEF transition differed from CAD(−) group and CAD(+) group, but further analysis is necessary with larger population. Currently, results are awaited from the PEARL study, lead by Komuro et al, which investigates the effect of pitavastatin on patients with chronic heart failure.

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ELSEVIER

Letter to the Editor

Buerger's disease-like vasculitis associated with Kimura's disease

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Abstract

A 46-year-old man was first diagnosed as Buerger's disease according to his clinical and radiological features because he had no evidence of parasitic, allergic and connective tissue disease. Soft subcutaneous nodules suspected of lymphadenopathy on the bilateral inguinal regions were recognized after admission. Positron emission tomography scan showed the increased uptake of ^{18}F-fluoro-2-deoxyglucose in the bilateral inguinal regions. We finally diagnosed him as Kimura's disease based on pathologic findings and laboratory data, and started steroid therapy. The uptake of ^{18}F-fluoro-2-deoxyglucose disappeared and his leg pain was improved after the treatment. This is the first case report presenting a patient of Kimura's disease with Buerger's disease-like vasculitis who was demonstrated by positron emission tomography.
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Keywords: Buerger's disease; Eosinophilia; Kimura's disease; Positron emission tomography; Prednisolone

1. Introduction

Buerger's disease (BD) is a nonatherosclerotic inflammatory disorder of unknown etiology that affects small and medium-sized vessels of the extremities. The diagnosis of BD requires the elimination of many other diseases because of the absence of specific diagnostic criteria. Kimura's disease (KD) is a rare chronic inflammatory disorder presenting subcutaneous masses predominantly in the head and neck region, and peripheral eosinophilia. Positron emission tomography (PET) scan is a powerful imaging technique in the diagnosis and follow-up of many diseases including cancer, infection and inflammation. We report a case of KD with BD-like vasculitis who was demonstrated by ^{18}F-fluoro-2-deoxyglucose (FDG)-PET.

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2. Case report

A 46-year-old man was admitted with a 1-month history of sharp rest pain in right calf. He had ischemic ulceration between the third and fourth toes of his right foot (Figs. 1A and 2A). He has smoked 10 cigarettes or less per day for 25 years. The digital subtraction angiogram of the extremities showed multiple occlusions of the distal arteries including right anterior tibial artery, right posterior tibial artery, right peroneal artery, left anterior tibial artery and left peroneal artery (Fig. 3). He was first diagnosed as BD according to his clinical and radiological features because he had no evidence of parasitic, allergic and connective tissue disease. Soft subcutaneous nodules suspected of lymphadenopathy on the bilateral inguinal regions were recognized after admission. No other lymph node was palpable. PET using FDG performed after overnight fasting and heparin sodium injection (2000 IU) revealed increased uptake of FDG in the bilateral inguinal regions (Fig. 4A). Since these lesions were considered as lymphoproliferative disorder, an excision biopsy of left inguinal nodule was performed. The pathology of the specimen revealed hyperplasia of lymphoid follicles
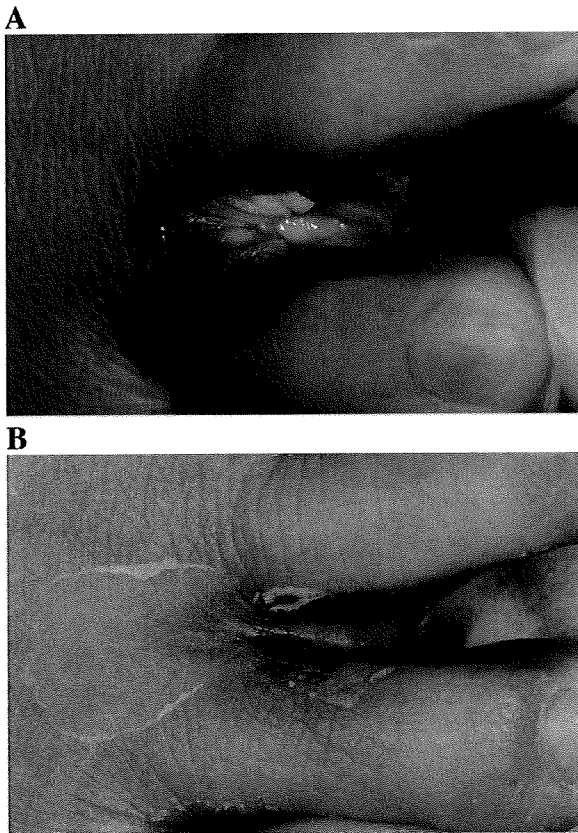
Fig. 1. Ischemic ulceration between the third and fourth toes of right foot (A) on admission and (B) after steroid therapy.

with germinal centers and massive infiltration of eosinophils without malignancy, which are typical findings of KD (Fig. 5A and B). Laboratory tests showed peripheral eosinophilia (WBC 20800, 56% eosinophils) and elevated serum immunoglobulin E level of 1921 U/mL. Screening for rheumatoid factor, anti-nuclear antibodies and ANCA were all negative. Protein C and protein S were within normal ranges. We finally diagnosed him as KD based on pathologic findings and laboratory data, and started the treatment with prednisolone 40 mg/day. After the treatment, eosinophilia, the ulcer and rest pain of right foot improved quickly (Figs. 1B and 2B). The FDG uptake in the bilateral inguinal regions disappeared after 4 weeks by the treatment with prednisolone (Fig. 4B).

3. Discussion

BD is a nonatherosclerotic inflammatory disorder of unknown etiology that affects small and medium-sized vessels of the extremities and has a strong association with smoking [1]. Typically, affected persons are young men and the symptoms appear before the age of 40 years old. Cessation of cigarette smoking is the only known effective therapy. The diagnosis of BD requires ruling out other diseases because of the absence of specific diagnostic criteria. KD is a rare chronic inflammatory disorder presenting subcutaneous masses predominantly in the head and neck region, peripheral eosinophilia and elevated serum immunoglobulin E level [2]. Histologically, lymphoid follicles formed from lymphocytes,
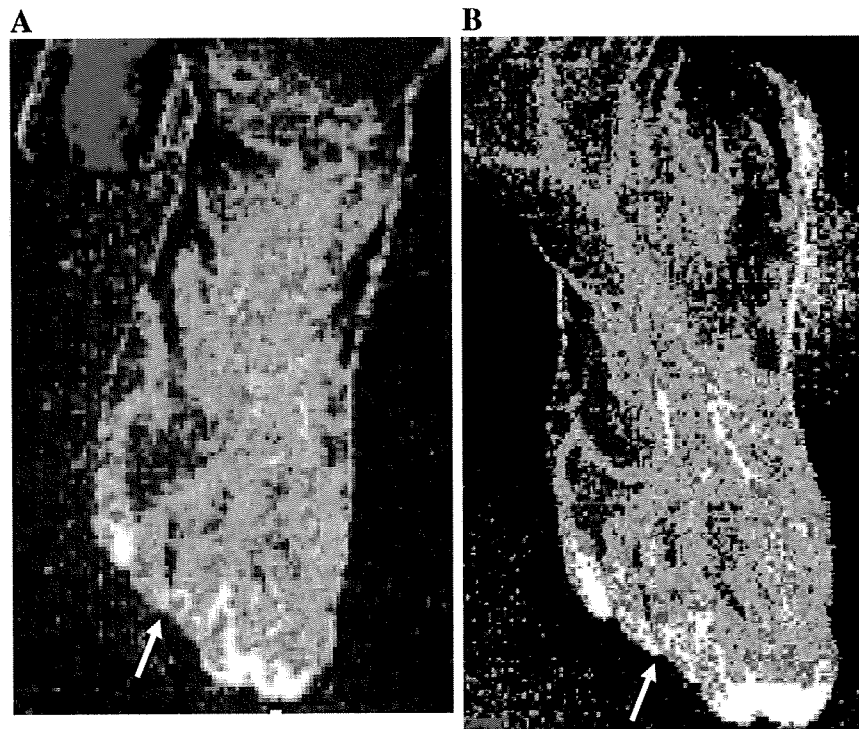
Fig. 2. Laser Doppler imaging of right foot (A) on admission and (B) after steroid therapy. Color-coded images represent blood flow distribution. The highest perfusion is displayed as white. The steroid therapy improved the peripheral blood supply (arrows).
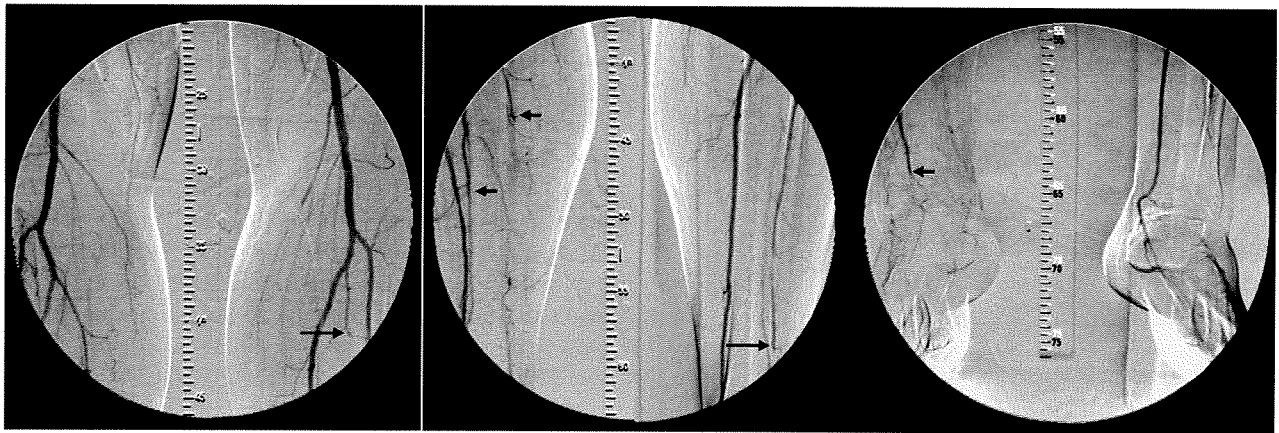
Fig. 3. Multiple occlusions of the crural arteries including right anterior tibial artery, right posterior tibial artery, right peroneal artery (arrowheads), left anterior tibial artery and left peroneal artery (arrows).

plasma cells and abundant eosinophils are characteristic. KD occurs endemically in Asian males. Renal abnormalities are associated with KD [3], but there is only one case on KD patient with BD [4]. PET scan is a powerful imaging technique in the diagnosis and follow-up of many diseases including cancer, infection and inflammation. Recently, the generalized lymphadenopathy was demonstrated in a patient with KD by FDG-PET [5]. In the present case, FDG-PET

showed the increased uptake of FDG in the bilateral inguinal regions, which disappeared after steroid therapy. Concomitantly, the pain and ulceration of his right leg were improved. To our knowledge, there is no report presenting a patient of KD with BD-like vasculitis who was demonstrated by FDG-PET. Although the pathogenesis of BD is still unknown, steroid therapy is effective to stabilize inflammation in the patients with BD-like vasculitis. Therefore, it is important to
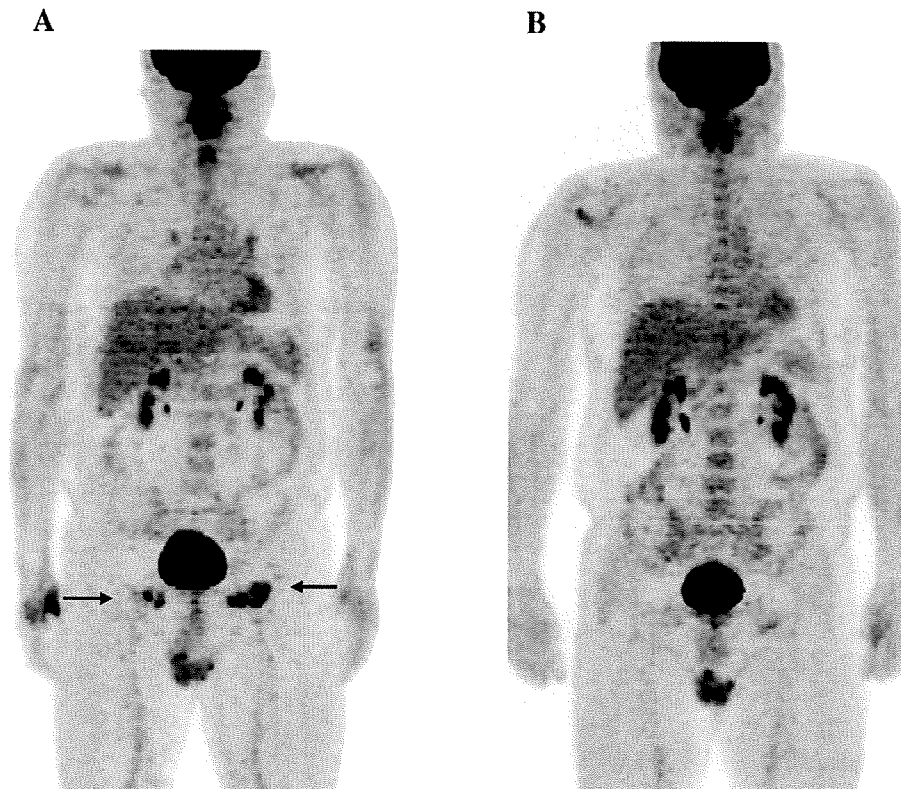
Fig. 4. FDG uptake (A) on admission and (B) after steroid therapy. The FDG uptake in the bilateral inguinal regions (arrows) disappeared 4 weeks after the steroid therapy.

A

B
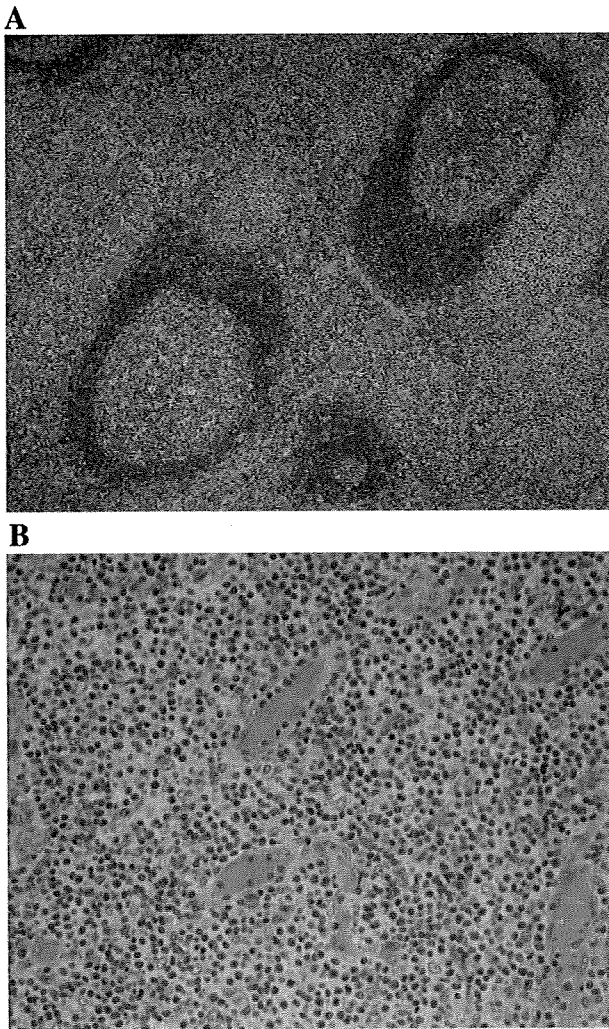
Fig. 5. Photomicrograph of the left inguinal nodule showed hyperplasia of lymphoid follicles with germinal centers and massive infiltration of eosinophils (hematoxylin and eosin staining). A, lower magnification, ×40. B, higher magnification, ×200.

examine the patients with vasculitis by FDG-PET whether they have lymphadenopathy or tumor-like lesion.

Acknowledgement

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Right-Sided Heart Wall Thickening and Delayed Enhancement Caused by Chronic Active Myocarditis Complicated by Sustained Monomorphic Ventricular Tachycardia

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A n asymptomatic healthy 65-year-old man was referred to a hospital for inverted T waves in the precordial leads (Figure 1) with paroxysmal advanced atrioventricular block in the ECG. Chest x-ray showed mild cardiac enlargement (Figure 2), and an echocardiogram showed right ventricular (RV) wall thickening (arrow in Figure 3). Five months later, the patient was referred to another hospital complaining of chest discomfort. Coronary angiogram was normal, but sustained monomorphic ventricular tachycardia (VT) occurred. Suffering from incessant VT, the patient was transferred to our hospital. The ECG and echocardiogram were almost the same as in previous studies. Enhanced multislice computed tomography revealed isolated right atrial, RV, and partial left ventricular (LV) wall thickening with extensive delayed enhancement (Figure 4) but no other organic diseases, which was confirmed by cardiac magnetic resonance (Figure 5).

In an electrophysiological study, 2 sustained monomorphic VTs (Figure 6) were induced, located in the RV midseptum by endocardial ventricular mapping. Radiofrequency ablation was performed at both sites; subsequently, neither VT could be induced. Because of the multislice computed tomography and cardiac magnetic resonance findings, endocardial biopsies were obtained from the RV (Figure 7) that showed interstitial edema, fibrosis, and myocyte destruction with a dense infiltrate of lymphocytes, suggesting chronic active myocarditis, which was consistent with his clinical course. Presumably, the thickening of the right atrial and RV free walls is related to lymphocytic infiltration and edema in the multislice computed tomography and cardiac magnetic resonance. A cardioverter-defibrillator was implanted, and the patient was given 40 mg/d prednisolone. He had no recurrent VTs after discharge.
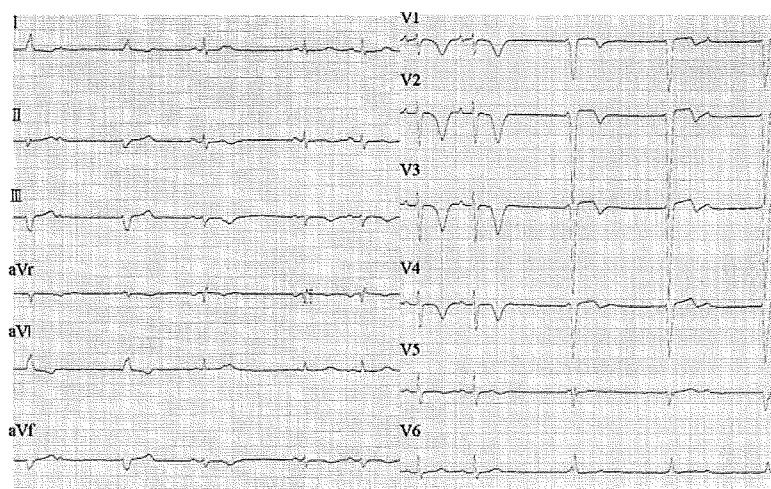
Disclosures

None.

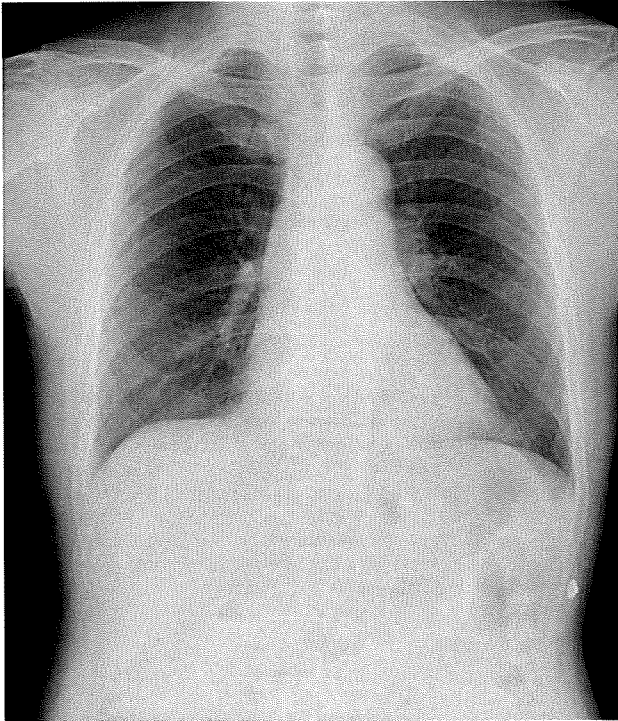**Figure 1.** ECG acquired when the subject was referred to hospital showed inverted T waves in the precordial leads.

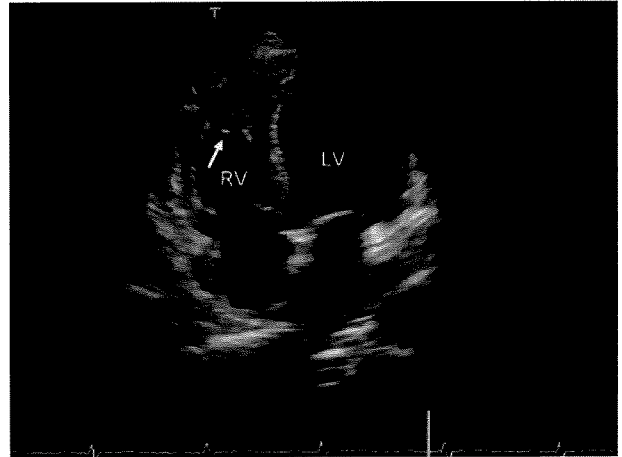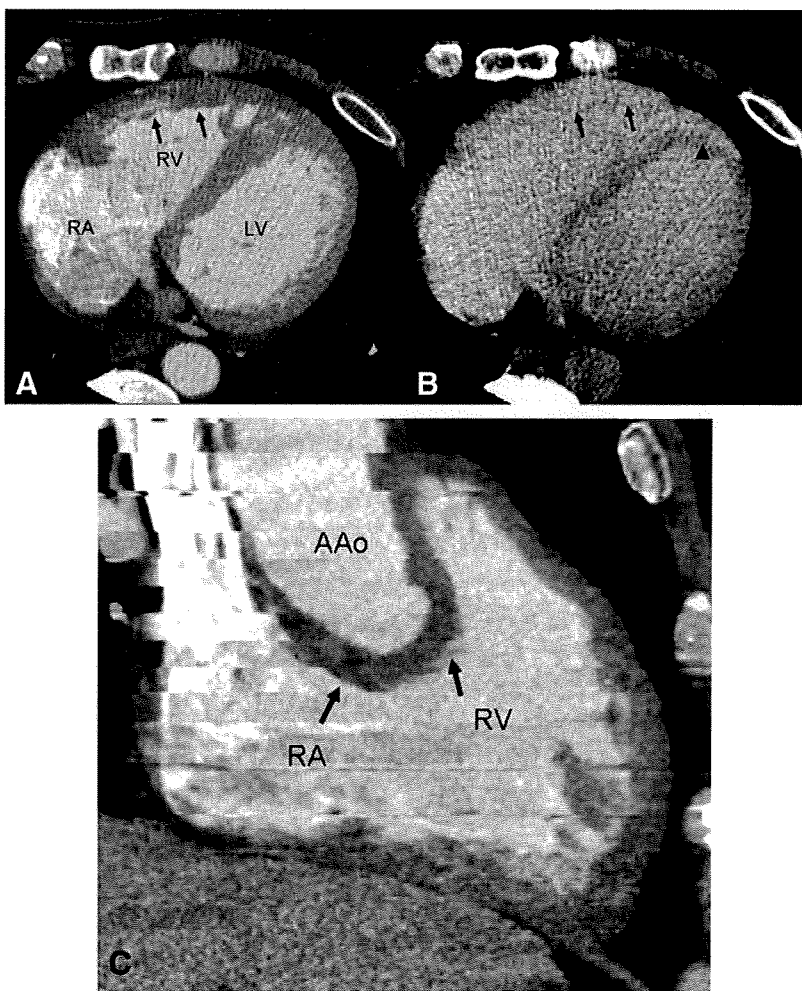**Figure 2.** Chest x-ray showed mild cardiac enlargement.

Figure 3. Transthoracic echocardiogram showed pericardial effusion and RV wall thickening (arrow) with no LV hypertrophy and normal systolic function of both ventricles.

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Figure 4. Axial source (A and B) and multiplanar reconstruction images (C) of enhanced multislice computed tomography revealed thickening of the right atrial (RA) and RV free walls (arrows in A and C) and part of the LV wall, which were abnormally enhanced in the later phase, as well as part of LV (arrows in B), suggesting lymphocytic infiltration and edema. AAo indicates ascending aorta.
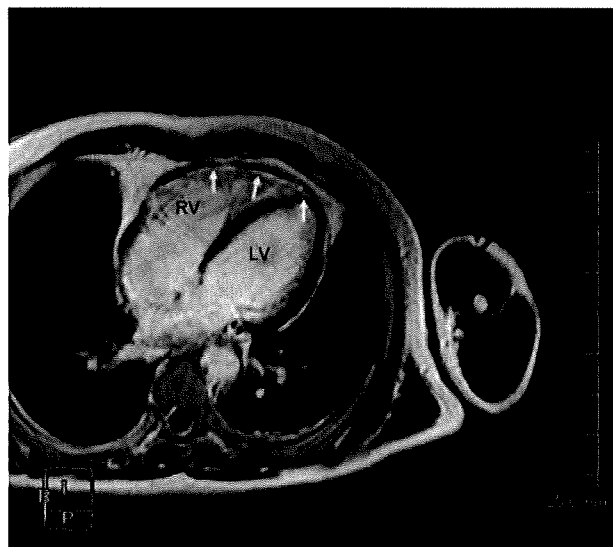
Figure 5. Cardiac magnetic resonance image revealed delayed enhancement (arrows) in the RV and part of the LV that was also observed in multislice computed tomography.

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VT1   VT2
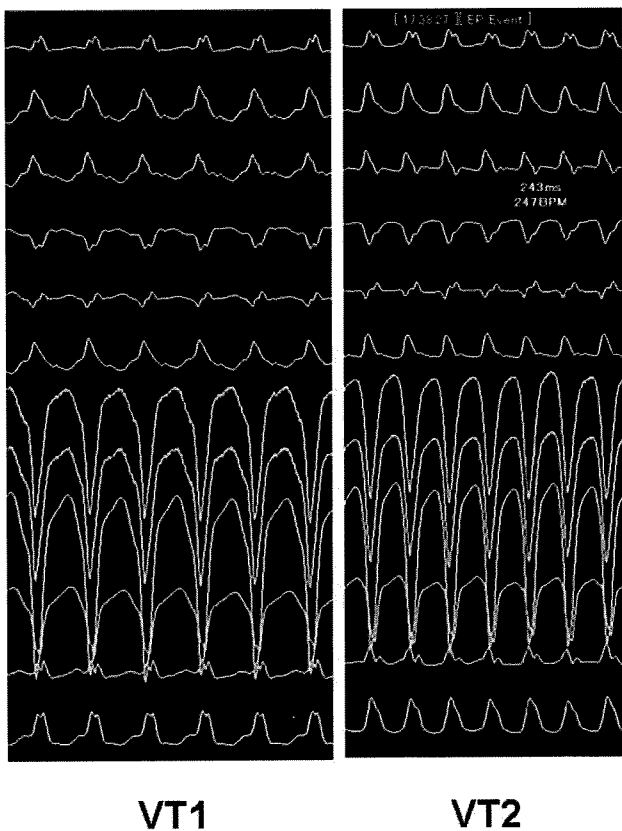
Figure 6. In an electrophysiological study, 2 clinical sustained monomorphic VTs were induced.
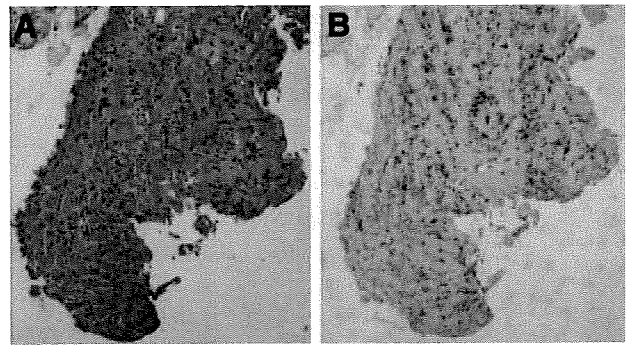
Figure 7. Histological results of endomyocardial biopsies. A, Hematoxylin and eosin staining demonstrated active myocarditis with focal lymphocytic infiltration with adjacent myocytolysis (×100). B, Immunohistological staining of T cells with focal infiltration pattern (×100).

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