Table 4: Stepwise Multiple Regression Analysis Predicting Contributors to Erythrocyte Filterability (N = 320)

model	F	R	P	Covariates (p)
1	2.650	0.259	0.008	Atrial fibrillation (0.023), Triglyceride (0.025), HbA1c (0.040), BMI (0.295) Current smoking (0.346), MCV (0.367), SBP (0.538), CKD (0.848)
2	3.034	0.259	0.004	Atrial fibrillation (0.023), Triglyceride (0.024), HbA1c (0.036), BMI (0.298) Current smoking (0.346), MCV (0.366), SBP (0.557)
3	4.077	0.273	0.001	Atrial fibrillation (0.004), Triglyceride (0.022), HbA1c (0.061), BMI (0.258) Current smoking (0.224), MCV (0.389)
4	4.748	0.269	< 0.001	Atrial fibrillation (0.003), Triglyceride (0.019), HbA1c (0.088), BMI (0.326) Current smoking (0.177)
5	5.835	0.265	< 0.001	Atrial fibrillation (0.002), Triglyceride (0.010), HbA1c (0.070), Current smoking (0.196)

F, F-value for fitness of multiple linear regression; P, probability for trend toward fitting the regression; p, probability of significant covariate contribution; R, multiple correlation coefficient. Other abbreviations are the same as in Table 1.

on the progression of CAD is not fully elucidated. In the present study, a highly sensitive and reproducible filtration technique was applied to the actual cardiac outpatients to assess the circulating intact erythrocyte filterability (whole cell deformability) in relation to coronary risk factors. Univariate analyses found significant impact of triglyceride (p = 0.004), HbA1c (p = 0.014), body weight (p = 0.020), and CKD (p = 0.041) on the impairment of the erythrocyte deformability, but multiple regression analysis demonstrated that nonvalvular AF was the greatest contributor to the impaired deformability, indicating that coronary risk factors including AF impair the erythrocyte filterability synergistically.

Erythrocyte Deformability and Coronary Risk Factors

It is generally accepted that erythrocyte deformability is determined by 1) erythrocyte membrane material properties; 2) internal density as reflected by MCHC; and 3) cellular geometric factors as reflected by MCV, surface-to-volume ratio and erythrocyte shape.[1] Therefore, abnormal erythrocyte membrane properties, increased MCHC or MCV, and several kinds of shape changes impair the deformability individually or in concert. There were no discernible erythrocyte shape changes in this study population. There were contributions of AF, triglyceride and HbA1c, but not of MCV or MCHC, to the deformability (Tables 3, 4). These findings indicate that impaired deformability mainly arises from erythrocyte membrane properties which may be altered by coronary risk factors such as hypertension, dyslipidemia, diabetes in addition to smoking.[10]

Erythrocyte membrane lipid components have profound influence on membrane fluidity and hemorheologic functions.[1] The present study demonstrated the association of impaired deformability with elevated serum triglyceride as in our previous study,[7] suggesting altered erythrocyte membrane integrity and lipid composition in hypertriglyceridemia.[12] Reportedly, our recent study clarified that diabetic erythrocytes show the impaired filterability and this impairment is enhanced by other risk factor such as smoking causing potent oxidative stress.[9,10] In this study, HbA1c is inversely proportional to the filterability (Table 3) and a marginal contributor to the impaired filterability (Table 4). Tsuda[13] demonstrated the increased erythrocyte membrane rigidity in hypertensive patients by electron spin resonance study. Therefore, the main cause of the impaired erythrocyte filterability is attributed to the erythrocyte membrane abnormalities in diabetic, hypertensive or dyslipidemic patients. Previous studies using this filtration technique (Fig. 1) clarified that deformability is markedly impaired in human erythrocytes exposed to acute oxidant stress.[14-16] Relative to such severe oxidant stress in vitro, mild oxidant stress in vivo as in above common diseases also causes persistent erythrocyte membrane lipid peroxidation and disturbs deformability.[9,17]

Erythrocyte Deformability in AF

Development of nonvalvular AF is known to be accelerated by risk factors common to those of CAD, because $CHADS_2$ and CHA_2DS_2-VASc scores predict not only the risk of ischemic stroke but also the new onset of AF.[18] Actually, more than half of enrolled patients are diabetic (69%), and one third of them are current smokers (37%) in the present study (Table 2). Moreover, major coexisting diseases are CKD (43%), hypertension (33%), dyslipidemia (32%) and CAD (15%). In this meaning, patients' profile of this study is similar to the Fushimi AF Registry, which is a Japanese domestic survey of AF patients conducted in urban community.[19]

AF is a common arrhythmia in clinical practice, and characterized by abnormal hemorheology in left atrium (LA) such as elevated hematocrit value and fibrinogen concentration.[20,21] Stagnant blood within the enlarged fibrillating LA appendage shows procoagulative state under erythrocyte hyperaggregability and elevated platelet reactivity.[22,23] Activated platelets release prostaglandin E2, which enhances calcium entry into erythrocytes leading to the impairment of erythrocyte deformability.[24,25] AF is associated with oxidant stress via increased LA wall superoxide production or angiotensin II type 1 receptor-mediated pathway.[26,27] Such local LA environment oxidizes erythrocytes and impairs the deformability.[15,16] Erythrocyte dynamics are improved by medication such as statin,[28] aspirin,[29] Ca antagonists[15,25] and eicosapentaenoic acid.[30] These agents were prescribed to AF patients associated with CAD for coronary risk reduction and rate control of AF. Such therapeutic effects may have attenuated the impairment of the erythrocyte deformability in AF patients in this study.

It is questionable whether AF is an independent risk of ACS.[31] Reportedly, total cholesterol content of erythrocyte membrane is increased in the patients with ACS,[32] which is ameliorated by statin therapy.[33,34] Increased cholesterol content reduces the erythrocyte membrane fluidity and impairs the deformability leading to erythrocytes aggregation and coronary flow slowing.[35,36] This study excluded patients with ACS, and the answer for this question awaits future cohort investigating erythrocyte deformability in ACS patients with AF and that in ACS patients without AF.

Limitations

This study has several limitations. First limitation is small sample of patients (n = 320) treated at the discretion of attending physicians. Nonvalvular AF with few episodes of paroxysms may

Table 5: Cross Table of Atrial Fibrillation and Coronary Risk Factors

	Hypertension (+)	Dyslipidemia (+)	Diabetes mellitus (+)	Current Smoking (+)
Atrial fibrillation (+) n = 33	24	20	18	16
Atrial fibrillation (–) n = 287	83	83	202	103
N = 320	n = 107	n = 103	n = 220	n = 119
p	< 0.001	< 0.001	0.063	0.156

n, number of subjects in a specific group; N, total number of subjects

Table 6: Effects of Coronary Risk Accumulation on Erythrocyte Filterability

Coronary Risk Factors	Erythrocyte Filterability (%)
no risk factor	88.8 ± 0.3
Hypertension	87.8 ± 0.3
Hypertension + Dyslipidemia	87.4 ± 0.4
Hypertension + Dyslipidemia + Diabetes mellitus	86.9 ± 0.7
Hypertension + Dyslipidemia + Diabetes mellitus + Smoking	86.3 ± 0.9
Hypertension + Dyslipidemia + Diabetes mellitus + Smoking + Atrial fibrillation	86.1 ± 1.0

Multiple comparison of the erythrocyte filterability during the stepwise accumulation of coronary risk factors showed highly significance ($p < 0.001$).

have been dismissed in this study population. Second limitation is a cross-sectional nature of study design. Coronary risk factors were considerably accumulated in the AF patients group in that average CHA_2DS_2-VASc score was 3.30 ± 0.24. However, unlike in the other study,[37] impaired erythrocyte deformability in AF patients could not be correlated to the ischemic stroke in this study partly due to intensive anticoagulation. Finally, erythrocyte filterability shows small intergroup differences and intragroup deviations (Tables 2 and 6). This is due in part to the aforementioned medication, but in other part due to high sensitivity and reproducibility of our methodology. Filtertability of erythrocytes obtained from healthy volunteers (positive control) was 88.8 ± 0.3% (Table 6), and that of erythrocytes exposed to severe oxidant stress was declined to 20% (negative control) leading to filter occlusion or hemolysis.[15] Therefore, our data presented in this study reflects mildly pathological human erythrocyte behaviors leading to impaired but not occluded microcirculation in vivo under treatments.

Conclusions:

This study investigated the intact human erythrocyte deformability in relation to coronary risk factors of actual cardiac patients. Multiple regression analysis showed that nonvalvular AF is unexpectedly and mostly attributable to the impaired erythrocyte deformability among other coronary risk factors, reflecting nonvalvular AF as an outcome of multiple coronary risk accumulations. Therefore, this small sample study should be validated by a future cohort to validate the important hemorheorologic role of erythrocytes playing in prothrombotic state leading to ischemic stroke associated with AF.

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Reduced Plasma Eicosapentaenoic Acid–Arachidonic Acid Ratio in Peripheral Artery Disease

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Abstract

A reduced ratio of plasma eicosapentaenoic acid–arachidonic acid (EPA-AA) is a newly recognized atherosclerotic risk factor. This ratio has not been fully investigated in peripheral artery disease (PAD). Seventy Japanese patients with atherosclerotic risk factors were enrolled and divided into 2 groups, those with PAD (group A: n = 38) and those without PAD (group B: n = 32). The EPA-AA ratio ($P = .001$) and ankle–brachial index (ABI: $P < .001$) in group A were significantly lower than those in group B. Univariate and multivariate analyses demonstrated that EPA-AA, ABI, and prescription of clopidogrel had significant correlation with PAD. Given the appropriate cutoff values, EPA-AA (odds ratio [OR] = 11.7, 95% confidence interval [CI] = 3.0-45.8; $P < .001$) and ABI (OR = 44.0, 95% CI = 5.4-358.5; $P < .001$) are factors independently associated with PAD. In conclusion, this study demonstrated that reduced plasma EPA/AA may underlie PAD at least in Japanese.

Keywords

ankle–brachial index, atherosclerosis, eicosapentaenoic acid, arachidonic acid, peripheral artery disease

Introduction

Peripheral artery disease (PAD) is one of the major atherosclerotic manifestations, showing progressive lipid, inflammatory cell, and fibrous matter accumulation in peripheral arteries in the lower extremities. Peripheral artery disease impairs not only the quality of life but also the long-term prognosis of patients with atherosclerosis due to the coexisting coronary artery disease (CAD), which is a major cause of mortality and morbidity in patients with PAD.

Reportedly, relative risk of dying in patients with PAD compared with that in controls is 3.1 for deaths from all causes, 5.9 for all cardiovascular deaths, and 6.6 for deaths from CAD.[1] An increasing body of evidence indicates that dietary intake of fish-derived polyunsaturated fatty acid shows favorable outcome in patients with CAD,[2,3]since plasma essential fatty acids and their profile exert protective effects against atherosclerotic progression. The Japan eicosapentaenoic acid (EPA) lipid intervention study (JELIS) showed for the first time that additive administration of purified EPA reduced coronary events by 19% in patients undergoing statin prescription.[4] Moreover, subanalyses of JELIS demonstrated that EPA reduced the incidence of recurrent stroke[5] and of CAD in patients complicated with PAD.[6]

Dietary essential fatty acids are classified into n-3 (eg, EPA) and n-6 (eg, arachidonic acid [AA]) groups, and the metabolites of these fatty acids have mutually opposing effects on CAD. Therefore, the balance of plasma n-3 and n-6 fatty acids is linked to the progression of CAD.[7] The plasma EPA-AA ratio is an atherosclerotic biomarker reflecting the intrinsic n-3/n-6 ratio. However, clinical studies investigating the association of plasma EPA-AA ratio with the incidence of PAD are limited.[8]

According to the JELIS trials,[4-6] we hypothesized that among other conventional atherosclerotic risk factors, the intrinsic plasma EPA-AA ratio plays a key role in the development of PAD that requires endovascular therapy. Therefore, the present study was designed to test this hypothesis.

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Patients and Methods

Participants

This study was approved by the Institutional Review Board concerning Ethics of Clinical Research and performed from March to September 2010, according to the Declaration of Helsinki (2001). Japanese patients who were referred to Kyushu University Hospital for thorough examinations of suspected atherosclerosis were consecutively nominated in this study. Among 81 hospitalized patients, 70 consecutive patients without the prescription for purified EPA (1800 mg/d) were finally enrolled. Informed consent was obtained from each patient after admission for acquisition of data concerning plasma EPA-AA ratio.

Ankle–brachial index (ABI) was evaluated routinely in our vascular laboratory (ABI Form, Omron-Colin, Tokyo, Japan) for all the hospitalized patients. ABI was assessed utilizing both the anterior and the posterior tibial arteries.[9] Additionally, 2 kinds of duplex ultrasonography (Xario, Toshiba Medical Systems, Otawara, Japan; iE33, Philips Electronics Japan, Tokyo, Japan) were applied routinely to bilateral carotid, renal, and peripheral arteries in lower extremities. When ultrasonography showed positive findings, a further imaging protocol was added for endovascular therapeutic strategies, that is, contrast-enhanced multidetector computed tomography (Aquilion TSX-101A, Toshiba Medical Systems) and 2 different superconductive magnetic resonance imaging units (Signa, General Electric Medical Systems, Milwaukee, Wisconsin; Magnetom Vision & Symphony Units, Siemens, Erlangen, Germany) were involved.

These patients showing atherosclerotic risk factors were divided into 2 groups, those with PAD (group A: n = 38) and those without PAD (group B: n = 32). Group A included patients with CAD (n = 20), carotid artery stenosis (n = 3), and renal artery stenosis (n = 6), whereas group B included CAD (n = 23). Endovascular therapy for PAD was successful in all the patients in group A.

Protocol

Baseline characteristics and drug prescriptions were investigated using medical records. Demographic variables, conventional atherosclerotic risk factors, plasma EPA-AA ratio, and prescription were analyzed in the 2 groups. Data collection and analyses were performed blindly by different physicians. Hypertension was defined as casual blood pressure ≥149/90 mm Hg and/or ongoing antihypertensive treatment.[10] Diabetes was defined as HbA_{1c} ≥6.5% and/or antidiabetic medication. Dyslipidemia was also defined as serum low-density lipoprotein (LDL) cholesterol ≥140 mg/dL, serum high-density lipoprotein (HDL) cholesterol <40 mg/dL or the prescription of lipid-lowering agents.[11] Medication included antiplatelet agents (aspirin, clopidogrel, cilostazol, and ticlopidine) for atherosclerosis, statins for dyslipidemia, antihypertensive agents (calcium antagonists, α-blockers, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) for hypertension, and hypoglycemic agents (sulfonylurea, metformin, and α-glucosidase inhibitors) for type 2 diabetes. Prescription was not altered in any patient during the study.

Data Analysis

Continuous data are expressed as means ± standard deviation, and categorical data are expressed as numbers (n) and percentage in parentheses. For continuous data, the normality of the distribution was examined by the Kolmogorov-Smirnov test. Intergroup comparison of continuous data was made by Student t test for normally distributed data, and by Mann-Whitney U test for other data. Comparison of continuous data among more than 2 groups was performed by analysis of variance (ANOVA) for normally distributed data, and by Kruskal-Wallis test for other data. Categorical data were analyzed by Fisher exact test or Pearson χ^2 test with Yates continuity correction, if necessary. The assumptions used for power calculations required a sample size of more than 20 patients per group without any dropout cases to provide 80% power to detect a 5.0% difference in plasma EPA-AA ratio, with a 5% type I error rate for a 2-sided test. Univariate analysis was conducted by Spearman rank correlation test. Baseline characteristics showing significant difference in univariate analysis were incorporated into multivariate analysis. Receiver–operating characteristic (ROC) curves providing cutoff values of EPA-AA and ABI were constructed. Practical computation was performed using Predictive Analytics Software (PASW) 18.0 version for Windows (SPSS, Inc., IBM, Chicago, Illinois). A 2-sided $P < .050$ was considered significant.

Results

Kolmogorov-Smirnov test demonstrated that distributions of plasma endogenous EPA-AA ratio ($P = .007$), ABI ($P < .001$), and serum high-sensitivity C-reactive protein (hsCRP; $P < .001$) were not normal. Table 1 shows comparisons of the demographic variables, distribution of atherosclerotic risk factors, laboratory data, and prescriptions between groups A and B. There were no differences in the incidence of hypertension, hyperuricemia, type 2 diabetes, dyslipidemia, CAD, and thoracoabdominal aortic aneurysm. Incidence of current smoking was equivalent. In laboratory investigations, plasma EPA concentration ($P = .008$), EPA-AA ratio ($P = .001$), and ABI ($P < .001$) in group A were significantly lower than those in group B, whereas the difference in plasma AA concentration between the 2 groups was marginal ($P = .050$), indicating that the significantly lower plasma EPA-AA ratio in group A is due mainly to the lower EPA concentration. On the other hand, hsCRP showed no significant intergroup difference ($P = .813$). Distribution and difference of plasma EPA-AA ratio are detailed in Figure 1. With respect to medication, prescriptions of clopidogrel ($P = .038$) and hypoglycemic agents ($P = .032$) in group A were significantly more frequent than those in group B.

Table 1. Comparisons of Demographic Variables Between Group A and Group B[a]

	Group A	Group B	P
N	38	32	
Age, years	69.8 ± 6.6	69.6 ± 9.2	.909
Sex, F/M	11/27	6/26	.322
BMI, kg/m^2	23.9 ± 3.4	24.3 ± 3.9	.607
Current Smoking, %	76.3	71.9	.672
Hypertension, %	89.5	93.8	.524
Diabetes mellitus, %	68.4	46.9	.068
HbA_{1c}, %	6.5 ± 1.0	6.2 ± 1.3	.433
Dyslipidemia, %	76.3	84.4	.401
TC, md/dL	178 ± 37	173 ± 35	.554
LDL-C, mg/dL	102 ± 29	97 ± 32	.495
HDL-C, mg/dL	47 ± 9	47 ± 12	.921
TG, mg/dL	148 ± 61.5	132 ± 70	.205
EPA, mg/dL	54.3 ± 25.3	69.7 ± 27.0	.008
AA, mg/dL	164.4 ± 40.2	146.6 ± 31.7	.050
EPA-AA ratio	0.33 ± 0.13	0.50 ± 0.22	.001
Hyperuricemia, %	31.6	21.9	.363
Uric acid, mg/dL	5.9 ± 1.6	6.2 ± 1.3	.400
hsCRP, mg/dL	0.54 ± 0.96	0.19 ± 0.25	.813
Serum Cr, mg/dL	1.38 ± 1.43	1.19 ± 1.31	.641
eGFR, mL/min/1.73 m^2	59 ± 23	61 ± 19	.513
ABI	0.84 ± 0.26	1.11 ± 0.10	<.001
CAD, %	52.6	71.9	.099
TAA-AAA, %	21.1	37.5	.129
Medication, %			
Aspirin	86.8	81.3	.522
Clopidogrel	52.6	28.1	.038
Ticlopidine	15.8	18.8	.743
Warfarin	5.3	6.3	.859
Cilostazol	15.8	3.1	.078
Statin	84.2	78.1	.514
Calcium blockers	47.4	53.1	.631
RAS inhibitors	60.5	68.8	.474
Hypoglycemic agents	50.0	25.0	.032

[a] Data are presented as percentage or mean ± standard deviation.
Abbreviations: AA, arachidonic acid; AAA, abdominal aortic aneurysm; ABI, ankle–brachial index; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; RAS, renin–angiotensin system; TAA, thoracic aortic aneurysm; TC, total cholesterol; TG, triglyceride.

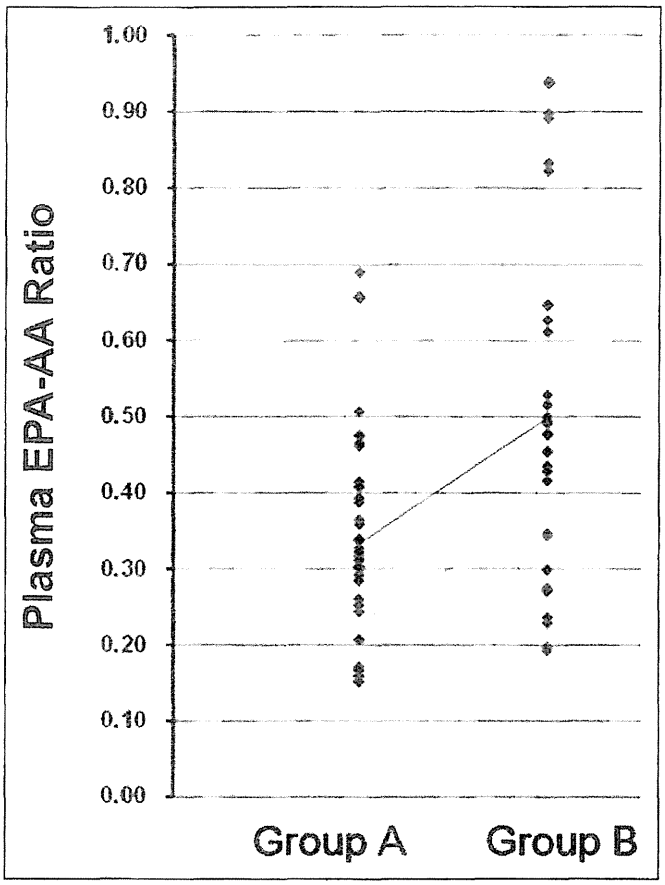

Figure 1. Distribution of the ratio of plasma eicosapentaenoic acid and arachidonic acid (EPA-AA). The EPA-AA ratio in group A (n = 38) was significantly (P = .001) lower than that in group B (n = 32).

Table 2. Univariate and Multivariate Analyses of Demographic Variables in PAD

	Univariate		Multivariate	
Variables	R	P	β	P
EPA-AA	−.427	<.001	−5.053	.018
ABI	−.548	<.001	−8.615	.001
Clopidogrel	.251	.039	−1.902	.014
Hypoglycemic agents	.256	.033	–	–

Abbreviations: AA, arachidonic acid; ABI, ankle–brachial index; EPA, eicosapentaenoic acid; PAD, peripheral artery disease.

Table 2 shows the results of univariate and multivariate analyses concerning PAD. In the univariate analysis, variables showing significance in Table 1 were investigated. As an essential fatty acid profile, EPA-AA ratio but not absolute plasma EPA concentration was adopted. Consequently, all variables revealed significant contribution to PAD. In multivariate analysis, plasma EPA-AA ratio (P = .018), ABI (P = .001), and prescription of clopidogrel (P = .014) remained as independent factors related to the presence of PAD. The relationship between plasma EPA-AA ratio and ABI was further examined (Figure 2). Linear regression of ABI (y) as a function of EPA-AA (x) was significant ($y = 0.366x + 0.812$, $r^2 = .089$; P = .013).

Analysis of ROC curves was performed to obtain the optimal cutoff values of plasma EPA-AA ratio and ABI for diagnosing PAD (Figure 3). The areas under the curve for plasma EPA-AA ratio and for ABI were 0.734 and 0.824, respectively. It is of note that ABI shows high specificity under a wide range of sensitivity. Optimal cutoff value of the EPA-AA ratio was 0.43 and that of ABI was 0.90 as addressed by meta-analysis.[12] Considering the high specificity of ABI, the cutoff value of the plasma EPA-AA ratio was set at 0.49 to improve its own sensitivity, whereas that of ABI was set at the optimal level (0.90).

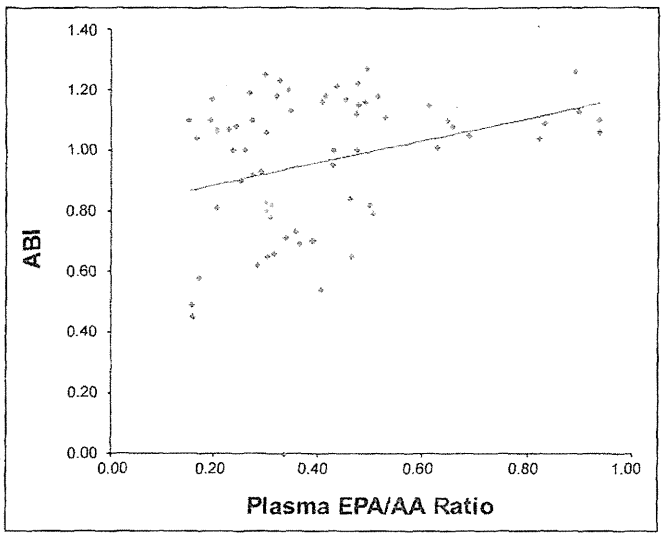

Figure 2. Relationship between plasma EPA-AA ratio and ankle–brachial index (ABI). ABI (y) is shown as a function of EPA-AA (x), yielding a linear regression of $y = 0.366x + 0.812$ ($r^2 = .089$, $P = .013$). EPA indicates eicosapentaenoic acid; AA, arachidonic acid; ABI, ankle–brachial index.

Table 3 shows the sensitivities and specificities of these 2 variables for the diagnosis of PAD under these cutoff values. It is of note that these 2 variables showed a sharp contrast, that is, sensitivity of EPA-AA was superior to that of ABI, while specificity of ABI was superior to that of EPA-AA, as in the literature.[12] Under these cutoff values, diagnoses of PAD by plasma EPA-AA ratio (odds ratio [OR] = 11.7, 95% confidence interval [CI] = 3.0-45.8; $P < .001$) and by ABI (OR = 44.0, 95% CI = 5.4-358.5; $P < .001$) were highly significant.

Plasma essential fatty acid profile is known as a common risk factor for PAD and CAD in the Edinburgh Artery Study.[8,13] In order to compare the diagnostic significance of EPA-AA ratio in PAD with that in CAD, these patients were subdivided as follows: patients with CAD and PAD (group A1: n = 20), those with PAD and without CAD (group A2: n = 18), those with CAD and without PAD (group B1: n = 23), and those with neither CAD nor PAD (group B2: n =9). Plasma essential fatty acid profile was compared among the 4 subgroups (Table 4). There were significant differences in plasma EPA concentration ($P = .032$) and EPA-AA ratio ($P = .002$) among the subgroups. Furthermore, given the same cutoff value as in PAD (0.49), sensitivity and specificity of this ratio concerning CAD were 74.1% and 23.3%, respectively. Sensitivity of this ratio for CAD tended to be lower ($P = .052$) than that for PAD, and specificity for CAD was significantly ($P = .016$) lower than that for PAD.

Discussion

In the present study, plasma endogenous EPA-AA ratio and conventional atherosclerotic risk factors were analyzed in 70 consecutive Japanese patients with (group A) or without (group B) PAD. This study showed that EPA-AA and ABI in group A were significantly lower than those in group B (Table 1) and were independently associated with PAD by multivariate analyses (Table 2). The EPA-AA (OR = 11.7, 95% CI = 3.0-45.8, $P < .001$) showed high sensitivity, and ABI (OR = 44.0, 95%CI = 5.4 – 358.5, $P < .001$) showed high specificity (Table 3). Because of the linear regression between EPA-AA and ABI (Figure 2), reduced plasma EPA-AA ratio may indicate an etiological insight into PAD.

A series of JELIS trials conducted in Japanese atherosclerotic patients demonstrated that adjunctive prescription of EPA (C20: 5n-3) reduced the incidence of major coronary events,[4] recurrent stroke,[5] and CAD in patients complicated with PAD.[6] However, there is limited data concerning direct relationship between essential fatty acid and PAD. In Western countries, Edinburgh Artery Study did not clarify the cross-sectional relationship of plasma EPA and the incidence of PAD by a population-based approach.[8] In contrast, strong association of plasma EPA-AA ratio with PAD was obtained by this study (Tables 2 and 3). This discrepancy seems to be attributable to the different ethnicity and study design. This is a case–control study using Japanese atherosclerotic patients. Ethnic difference in essential fatty acid profile depends greatly on fish consumption.[14] Baseline EPA-AA ratio in Japanese is greater than that in Westerners,[15] which makes international comparison of domestic lipid investigations difficult. The Edinburgh Artery Study demonstrated that n-3 fatty acids, especially docosapentaenoic acid (C22: 5n-3),[16]exert protective effects against PAD.[8] Although diagnosis of PAD in a population approach is limited to history taking and ABI estimation,[17] their findings are compatible with those of this study, that is, the essential fatty acid profile remained as an independent factor related to PAD (Table 2).

Atherosclerotic prevention by additive administration of purified EPA is evident.[4,6] Metabolites of AA (C20: 4n-6), such as leukotriene B4, have proinflammatory effects, whereas n-3 fatty acids, such as EPA and docosahexaenoic acid (DHA; C22: 6n-3), antagonize AA cascade and show vasodilating, antiplatelet, and antithrombotic actions leading to prevention of atherosclerosis.[18-20] Both EPA and DHA have been shown to reduce cardiovascular mortality possibly mediated by improving the plasma lipid profile, endothelial function, and attenuating inflammatory or oxidative stress.[20] Moreover, n-3 fatty acid intake has been shown to improve hemorheology such as blood and plasma viscosity,[21,22] platelet function,[21,23] and erythrocyte deformability.[21,24] These favorable biochemical, hematological, and hemorheologic effects of n-3 fatty acid exert synergistic protective action against CAD and PAD. It is reported that EPA-AA relates to the severity of CAD,[25,26] which is partly confirmed in the present study (Table 4). Platelet function is reported to be more activated in PAD patients than in CAD patients, which is probably due to diffusely injured systemic arterial bed in PAD.[27] Activated platelets lead to their aggregation that is sensitive to EPA.[22] Platelet aggregation is deeply involved in atherothrombotic progression by multiple pathways mediated by thromboxane A2, adenosine

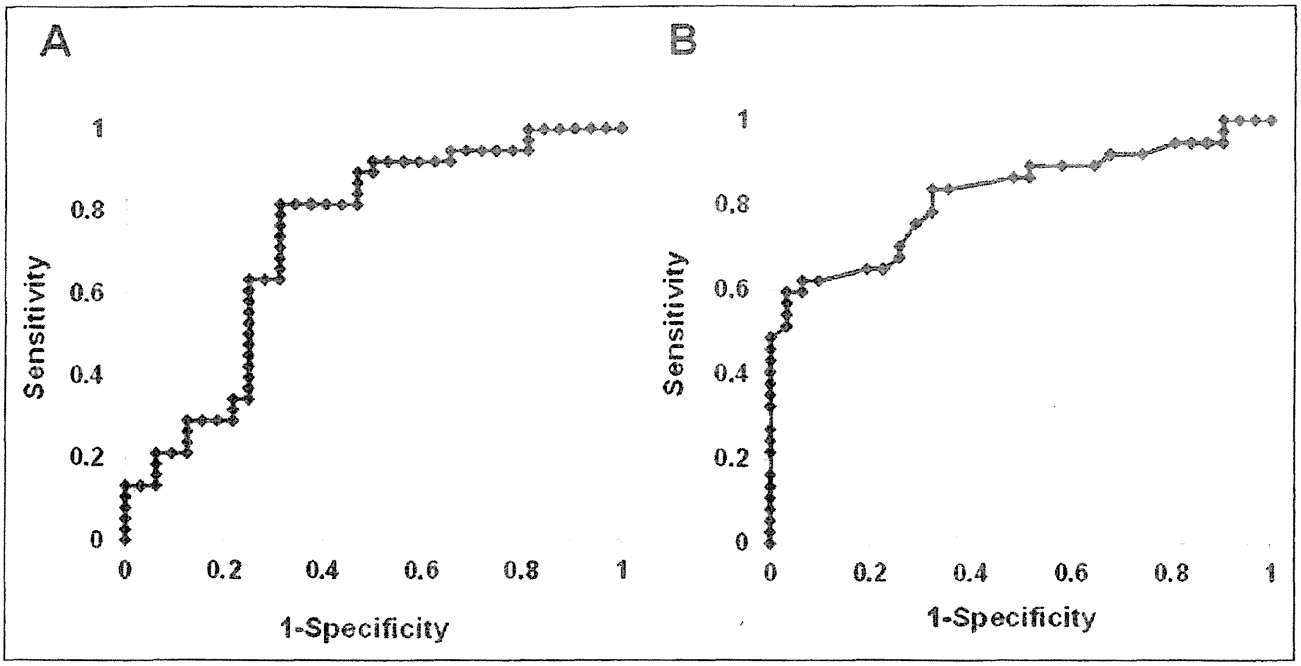

Figure 3. Receiver–operating characteristic curves for diagnosis of PAD by plasma EPA-AA ratio (A) and ABI (B). Area under the curve for EPA-AA is 0.734, and that for ABI is 0.824. EPA indicates eicosapentaenoic acid; AA, arachidonic acid; ABI, ankle–brachial index; PAD, peripheral artery disease.

Table 3. Comparison of Plasma EPA-AA Ratio and ABI in PAD

		PAD						
		(+)	(−)	Total	Sensitivity (%)	Specificity (%)	OR	95% CI
EPA-AA	<0.49	35	16	51				
	≥0.49	3	16	19	92.1	50.0	11.7	3.0-45.8
	Total	38	32	70				
ABI	<0.90	22	1	23				
	≥0.90	15	30	45	59.5	96.8	44.0	5.4-358.5
	Total	37	31	68				

Abbreviations: AA, arachidonic acid; ABI, ankle–brachial index; CI, confidence interval; EPA, eicosapentaenoic acid; OD, odds ratio; PAD, peripheral artery disease.

Table 4. Comparisons of Essential Fatty Acid Profile in 4 Subgroups[a]

	A		B		
Subgroup	A1	A2	B1	B2	*P*
PAD	(+)	(+)	(−)	(−)	
CAD	(+)	(−)	(+)	(−)	
n	20	18	23	9	
EPA, μg/mL	47.9 ± 18.7	62.4 ± 29.7	67.7 ± 27.4	74.8 ± 26.6	.032
AA, μg/mL	161.1 ± 44.2	168.1 ± 36.0	145.7 ± 35.0	148.7 ± 22.9	.229
EPA-AA	0.30 ± 0.11	0.37 ± 0.14	0.50 ± 0.25	0.51 ± 0.17	.002

Abbreviations: AA, arachidonic acid; CAD, coronary artery disease; EPA, eicosapentaenoic acid; PAD, peripheral artery disease.
[a] Data are presented as number of patients or mean ± standard deviation.

diphosphate, and platelet-derived growth factor.[28] These indicate that EPA-AA improvement may exert protective action against both PAD and CAD.

This single-center study has limitations due to small samples analyses and cross-sectional design. Therefore, this study does not guarantee the predictive value of EPA-AA ratio

for future development of PAD in atherosclerotic patients. Incidence of smoking was equivalent between the 2 groups in this study (Table 1). However, dietary intake of polyunsaturated fatty acids is well known to prevent atherosclerotic disease.[2,3] Antioxidative vitamin supplementation also has potential impact on the prevention and suppression of PAD.[29] Therefore, nutritional background should have been matched more strictly.

In conclusion, the present study has indicated that plasma EPA-AA ratio and ABI are 2 factors independently associated with PAD at least in Japanese atherosclerotic patients. Because of the linear regression between EPA-AA and ABI, reduced plasma EPA-AA may underlie PAD. However, it is unclear in this study whether reduced plasma EPA-AA ratio as a newly recognized lipid biomarker predicts future development of PAD. Therefore, prospective studies are required to resolve this issue.

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Declaration of Conflicting Interests

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インスリン抵抗性心筋症の概念と実態

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Concept and Real World of Insulin-Resistant Cardiomyopathy

Toru MARUYAMA[1)]*, Yumiko SAKAI[2)], Seiho NAGAFUCHI[3)]*

Abstract

Myocadium selects metabolic substrates, and energy cost efficiency is different among these substrates. The general concept that is widely accepted to date is that myocardial substrate selection (so-called metabolic switch) is impaired under the pathological conditions such as heart failure and myocardial ischemia. So far, direct correlation between insulin resistance and mechanical cardiac performance has been poorly understood. Insulin resistance causes hypertension, hyperglycemia, dyslipidemia and sympathetic acceleration, and all these abnormailties increase cardiac workload. Therefore, cardiac energy demand-supply imbalance occurs due to impairment of myocardial glucose uptake and subcellular insulin signaling. Such myocardial metabolic dysregulation causes subclinical heart failure, and this situation is currently defined as insulin-resistant cardiomyopathy. This type of cardiomyopathy is visualized by cardiac imaging techniques such as positron emission tomography and magnetic resonance imaging, showing myocardial triglyceride accumulation (cardiac steatosis) and impaired glucose uptake in spite of preserved coronary perfusion. Therapeutic intervention to this cardiomyopathy is expected by life style normalization and drug intervention such as glucagon-like peptide-1 (DLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) antagonists.

Key Words: Cardiomyopathy, Heart failure, Insulin resistance, Myocardial substrate metabolism

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はじめに

近年わが国ではメタボリック症候群の蔓延によってインスリン抵抗性という概念が社会的にも普及しつつある。インスリン抵抗性は代謝面で糖尿病を発症させ、循環系では血圧を上昇させ動脈硬化を進展させる。これらの一連の変化は心筋梗塞をはじめとする冠動脈疾患の発症につながる。しかしインスリン抵抗性と心筋疾患の直接的な関連はこれまでさほど注目されてこなかった。最近インスリン抵抗性が心筋のエネルギー源である基質の選択を誤らせ、糖の取り込みとインスリンシグナルを阻害し、また心筋への脂肪沈着を介して心機能を低下させ、これらは心不全の一因となることが知られるようになってきた。一方で心筋自体に病因が存する肥大型心筋症や拡張型心筋症などの特発性心筋症においても広くインスリン抵抗性が存在し、これら心筋症の予後を左右している。今回このような現状を踏まえてインスリン抵抗性と心筋疾患の複雑な関係を見直して、インスリン抵抗性心筋症の概念と実態を探ってみたい。

心筋のエネルギー基質

心臓は生体で最もエネルギー代謝が活発な臓器であり、一日5 kgのATPを消費している。心筋のエネルギー代謝の特徴はそれだけでなく、複数のエネルギー基質を利用できることにある。一般に心筋が利用する基質は遊離脂肪酸（FFA）が60-70%、単糖類が20%、乳酸が10%程度である[1]。すなわち心筋は代謝環境によってエネルギー基質を選択できる特性を備えており、空腹時にはFFAを、満腹時には摂取したグルコースを、運動後には骨格筋で生成された乳酸を主に利用し、状況に応じて利用すべき基質を変換している（metabolic switch）。

心筋代謝の基質である糖質と脂質を比較すると、そのエネルギー効率の違いが明らかである。脂質はほとんど炭素鎖（$[CH_2]_n$-）で構成され酸素原子が少ない。そのため分解されるには多くの酸素を要する。換言すると酸素消費量の割りにCO_2の産生量が少ないため呼吸商が小さい。逆に炭素原子が多いため単位重量当たりに発生する熱量が高く、好気的条件下で安定的に供給されれば優れたエネルギー基質であるといえる。一方の単糖類（$C_6H_{12}O_6$）は酸素原子が多いため酸素消費量が少なく呼吸商が大きい。しかし相対的に炭素の含有量が少ないために単位重量当たりの熱量産生は小さい（表1）。すなわちストレス環境下でも利用しやすい当座のエネルギー基質であり、生理的に血中酸素飽和度が低い胎児の心筋も酸素をさほど必要とせずに利用できる単糖類をエネルギー源とする。すなわち心臓は自身や全身の状況に応じてmetabolic switchを常に調節していることになる。しかし心筋は自身が病的な状態であったり、全身性の代謝疾患で基質のアンバランスが生じると基質選択性が低下したり（metabolic switchの変調）、基質選択の余地が無くなったり、基質の細胞内への取り込みが障害されたり、細胞内での利用障害が起きて中間代謝産物が心筋細胞内へ蓄積することにより心機能障害をきたすことになる[2-3]。

インスリン抵抗性と心筋代謝

インスリン抵抗状態になると交感神経系が活性化され、肥満が生じ、血液粘度は上昇して血液凝固能が亢進する。これらは心負荷となって心仕事量を増加させる。同時にインスリン抵抗性は心筋を高血糖や高FFA血症の代謝環境に曝すことになる。このようなストレス環境下では呼吸商が高くエネルギーコストが良い単糖類を基質として利用する方が心筋は有利である。したがって心筋は単糖類要求性にmetabolic shiftを起こすことになる。しかし実際にはインスリン抵抗状態のもとで心筋細胞膜上のグルコース輸送担体（GLUT4）の発現は抑制され、グルコースの取り込みが低下している。実際、GLUT4をノックアウトした遺伝子改変動物では心筋細胞肥大と線維化、心筋細胞内のCa^{2+}ハンドリングの異常と心収縮力の低下が見られる[4]。またインスリン抵抗状態ではインスリンシグナルの下流にあるAkt-1活性が阻害される。このためFFAの代謝酵素の活性化が起こり、心筋はエネルギーコストの悪いFFAを基質として利用しやすくなり、その脂質中間代謝産物も細胞内に蓄積しやすくなる（脂肪毒性）[5-6]。

インスリン抵抗性と心筋症

インスリン抵抗状態における心筋代謝の概要が今日明らかになりつつあるが、心筋自体に病因をもつ種々の心筋症がインスリン抵抗性を有するか否かは重要な問題である。心筋症には特発性心筋症と二次性心筋症があるが、狭義の心筋症である特発性心筋症とは心筋自体に病因があり、これによる心機能障害をきたす疾患群である。特発性心筋症の代表格は肥大型心筋症と拡張型心筋症である。Murakamiらは明らかな糖尿病や高血圧のない肥大型心筋症で、HOMA-IRを指標とした

表1. 三大栄養素の基質としてのエネルギー効率

三大栄養素	呼吸商*	単位重量当たりの発生熱量（kcal/g）
脂質	0.71	9.3
糖質	1.00**	4.1
タンパク	0.85	5.3

* 単位時間当たりのCO_2排出量/単位時間当たりのO_2消費量

** 単糖類では、$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$となり呼吸商は1

インスリン抵抗性がみられることを報告している。インスリンにはtrophic effectがあり、慢性的な高インスリン血症ではインスリンシグナルを介して、心筋細胞の肥大や間質の線維化が生じると考えられる。さらにMurakamiらは肥大型心筋症におけるインスリン抵抗性が左室内圧較差や突然死とも相関することを示した[7]。一方われわれは拡張型心筋症におけるインスリン抵抗性を検討してきた。明らかな心筋虚血がなくインスリン抵抗性を修飾する薬剤も投与されていない特発性拡張型心筋症、これと同程度の心機能を有する心臓弁膜症および健常者の三群でHOMA-IRを比較すると、拡張型心筋症でHOMA-IRが有意に高く、これは年齢やBMIで補正しても同様であった[8]。同様の報告は他にもあり、拡張型心筋症におけるインスリン抵抗性は拡張型心筋症の第一選択薬であるβ遮断薬で改善されることも明らかとなっている[9]。したがってインスリン抵抗性は特発性心筋症で広く存在し、それらの病態や予後に深く関与することが推察される。

インスリン抵抗性心筋症

既存の特発性心筋症の多くはインスリン抵抗性を示す一方でインスリン抵抗性と心不全には密接な関連があり、インスリン抵抗性は心不全のリスク要因となりその予後を規定する。一般に心負荷状態では糖質を主なエネルギー源とし、胎児心筋がそうであることから「胎児化現象」と呼ばれる。しかしインスリン抵抗状態では心筋細胞膜におけるGLUT4の発現が低下し、グルコースの心筋への取り込みが抑制される。加えて心筋細胞内のインスリンシグナルも阻害されるため、熱量発生の高い脂質を主に基質として利用している。これは心筋酸素消費量を増大させ、脂質中間代謝物を心筋細胞内へ蓄積させ、その脂肪毒性は心筋細胞のアポトーシスを惹起し、心機能を障害する[10]。すなわちインスリン抵抗状態においては高血糖状態や心筋におけるmetabolic switchのグルコース要求性（胎児化現象）にもかかわらず脂質を利用せざるを得ない状況にあり、酸素消費量は増大してエネルギーコストが悪化することになる。これらは臨床的にもPETやNMRを用いた画像診断で明らかになりつつある。インスリン抵抗状態では血流豊富な心筋組織でもグルコースの取り込みが低下する現象がPETにより確認されている[11]。また心機能障害がない段階でもNMRで評価した心筋の中性脂肪含量は耐糖能障害例で健常者の2.3倍、糖尿病例で2.1倍であることが報告され、インスリン抵抗性が糖尿病の発症や心機能障害に先行して心筋に中性脂肪の蓄積を引き起こしている実態も明らかになった[12]。これらの画像診断を利用した臨床研究から、インスリン抵抗性心筋症という概念は心不全が顕在化する前の前臨床段階で、われわれがすでに遭遇していた病態と考えられるようになった[11]。

表2. 日本人の諸疾患におけるインスリン抵抗性

対象	n	M/F	age	HOMA-IR
HOCM[1]	20	16/4	57.3 ± 2.1	3.57 ± 0.34
HNOCM[1]	35	30/5	56.7 ± 1.7	2.52 ± 0.14
DCM[2]	14	9/5	57.9 ± 2.0	3.54 ± 0.53
透析例[5]	52	41/11	63.8 ± 1.4	—
A	40	—	—	2.6 ± 0.5
B	12	—	—	3.6 ± 1.4
健常者[2]	15	9/6	62.2 ± 1.9	1.52 ± 0.51

A: インスリン非使用例、B: metabolic syndrome、DCM: 拡張型心筋症、HNOCM: 非閉塞性肥大型心筋症、HOCM: 閉塞性肥大型心筋症、HOMA-IR: Homeostasis Model Assessment-Insulin Resistance. (means ± SEM)。

インスリン抵抗性心筋症と心不全

近年、心不全の疾患概念が変わりつつある。従来自覚症状が出現してから初めて診断された心不全は現在、その危険因子を有するステージA、無症候性のステージB、有症候性のステージC、難治性心不全のステージDとステージ分類され、治療介入がなされなければより重症のステージへと移行する進行性の病態であると考えられている[13]。画像診断技術の進歩でインスリン抵抗状態での心筋代謝異常を視覚的にとらえることが可能になった現在、インスリン抵抗性心筋症は潜在性心不全のリスク要因というより心不全自体の早期ステージを表現しているといえよう。

血液透析例では心筋症類似の心血行動態を示す例が

ある。その多くは拡張型心筋症様の病態を呈しており、広く透析心と呼ばれている。これには高血圧、腎性貧血や動静脈シャントによる容量負荷などの様々な要因が関係している。しかし透析例の死亡原因の約2割が心不全で、その多くは無症候性の心不全である。血行再建術がなされても突然死などの心臓死を引き起こしやすいので透析心の病態解明は急務であるといえる。Nishimuraらは透析例における心臓死の関連因子を多変量解析で検討している。その結果、脂肪酸アナログであるBMIPPを用いたSPECTでのBMIPPスコアとインスリン抵抗性の指標であるHOMA-IRの二つの指標および年齢とBMI低値が心臓死の関連因子であったと報告している[14]。これから明らかな点は、透析例ではインスリン抵抗性による糖利用の抑制とFFAの代謝障害の両者があるために利用可能なエネルギー基質が大きく制限され、心筋エネルギー産生が著しく低下していることであろう。

表2に日本人の心腎疾患におけるインスリン抵抗性を示す。先に述べた肥大型心筋症や拡張型心筋症以外にも透析例では明らかなインスリン抵抗性を示しており、この現象はメタボリック症候群を合併した透析例ではさらに顕著になるとされている[15]。しかしこのインスリン抵抗性は透析自体に起因するのか、透析導入にいたる腎疾患にも起因するのか、広い意味での心腎相関をみているのかは不明である。また透析心不全にインスリン抵抗性心筋症がどの程度関与しているのか、実態は明らかではない。透析心では動静脈シャントによる心臓への容量負荷、二次性アミロイドーシスの影響、副甲状腺ホルモンによる心筋細胞内へのCa^{2+}の過剰負荷など透析特有の影響もあり、病態は複雑であるが早急な病態解明が必要である[16]。

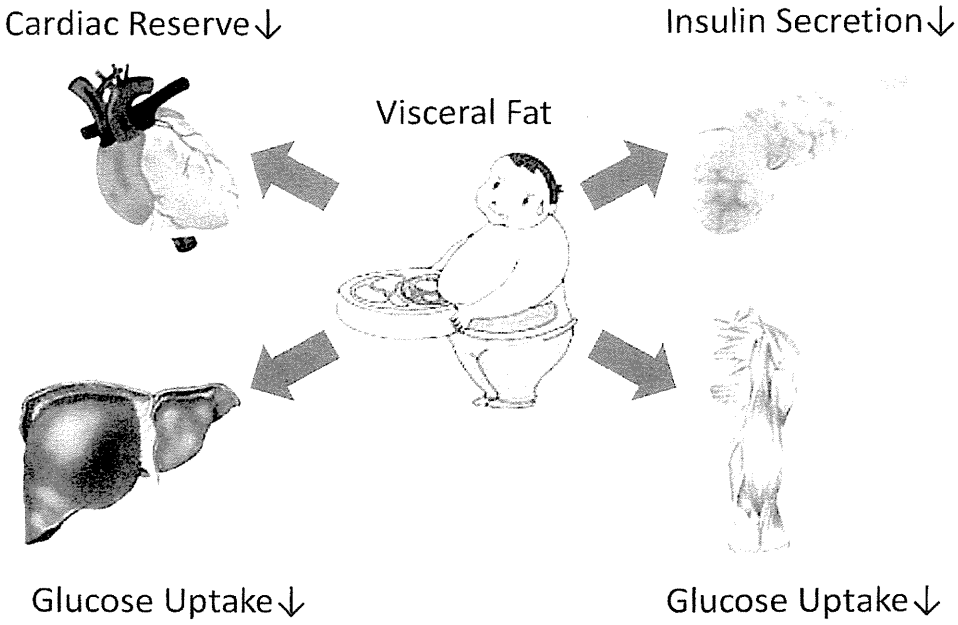

Figure 1: Physiological effects of visceral fat on various organs.

インスリン抵抗性心筋症と異所性脂肪蓄積症

元来農耕民族を祖先にもつ日本人は、欧米人と異なり皮下にのみ過剰の脂肪組織を蓄えることは困難である。余剰な脂肪は内蔵脂肪として蓄積し、さらに骨格筋、肝臓、膵臓、心臓などにも異所性に蓄積し、各臓器本来の機能を障害する（図1）。骨格筋の脂肪沈着は糖の取り込みを阻害し、インスリン感受性をさらに低下させる。膵臓の脂肪沈着は膵β細胞のインスリン分泌を低下させるのみならず、急性膵炎を引き起こし、時に致命的となる。インスリン抵抗性心筋症も異所性脂

肪蓄積症のひとつとしてとらえることができるが、近年この観点からインスリン抵抗性心筋症と類似した概念が提唱されている。McGavockらは2型糖尿病の発症時期におけるインスリン抵抗性と潜在性の左心機能低下、心筋中性脂肪含量の増加を特徴とするcardiac steatosisという概念を提唱した[17]。心筋への過剰な中性脂肪浸潤が心機能を著明に低下させることは、細胞内脂肪分解酵素adipose triglyceride lipaseの欠損症である中性脂肪蓄積心筋血管症（triglyceride deposit cardiomyovasculopathy）が拡張型心筋症様の重症心不全を呈し、2008年に初めて本邦での心移植待機例から見出されたことからも理解される[18]。

1970年代から高血圧や冠動脈病変のない糖尿病における心機能低下例に対して糖尿病性心筋症という概念が用いられてきた[19-21]。糖尿病性心筋症の病因には微小冠循環障害、糖尿病に起因する心筋の酸化ストレス、心臓自律神経障害など複数の要因が指摘されている。近年Rubinらは冠動脈疾患と顕在性心不全のない例でHbA1cと高感度心筋トロポニンT（hs-cTnT）の関係を解析し、両者には有意な正相関があり、既知の冠危険因子を補正するとHbA1cが5.7%未満の群に対して、HbA1cが5.7～6.4%の群と6.5%以上の群はhs-cTnT上昇のオッズ比がそれぞれ1.26と1.97であったと報告している[22]。すなわちこれから持続する高血糖と無症候性の心筋障害との直接的な関係が示唆される（糖毒性）。慢性的な高血糖の基盤にインスリン抵抗性があり、インスリン抵抗性が心筋のmetabolic shiftを起こして心機能を低下させるという点で、インスリン抵抗性心筋症とは糖尿病性心筋症をより踏み込んだ形で表現した病態概念であるといえる[23]。

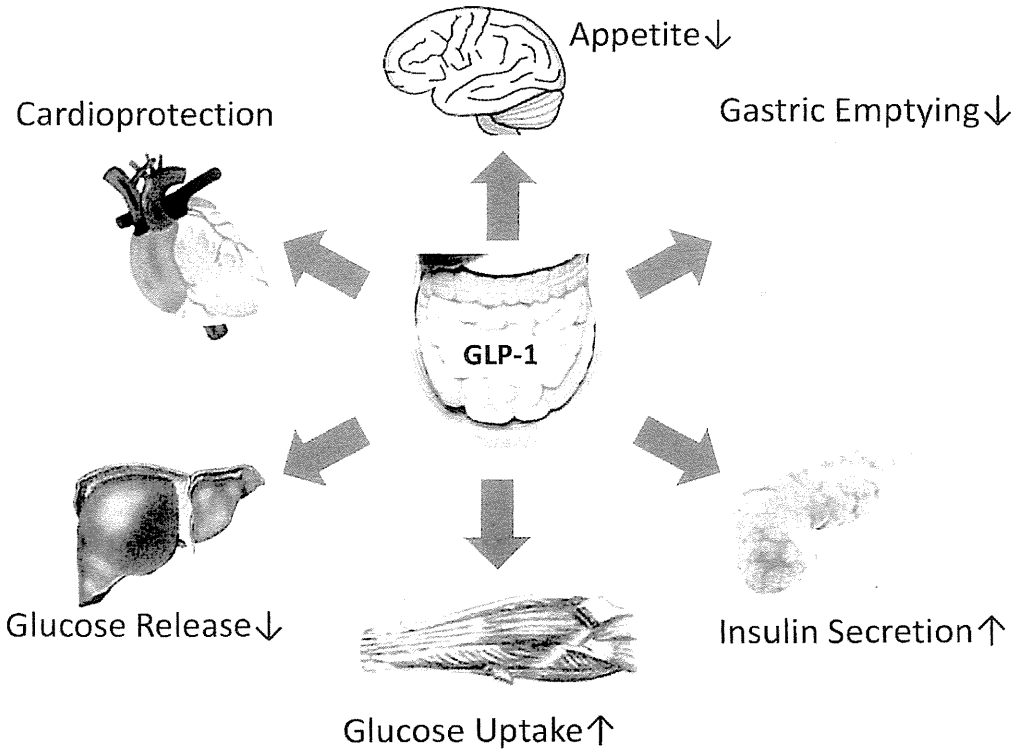

Figure 2: Physiological effects of GLP-1 on various organs.

インスリン抵抗性心筋症の治療

インスリン抵抗性心筋症は、その根底にあるインスリン抵抗性の改善が治療の第一歩である。食生活の欧米化や過栄養、運動不足、不規則な生活リズムや睡眠時間の短縮などによりインスリン抵抗性は日本人にますます浸透してきている。そこで食事療法や運動療法を中心とした生活指導・保健指導が基本的に重要である。これらの生活介入が困難な場合や健康支援のみではインスリン抵抗性の改善を認めない場合、インスリン抵抗性を標的とした薬物治療が必要となる。

PPAR-γは脂肪細胞の分化や肥大化をコントロールするマスター遺伝子であり、同時に脂肪蓄積を調節する

転写因子もほとんどがPPAR-γの標的遺伝子である。PPAR-γをノックアウトした遺伝子改変動物では強いインスリン抵抗性と動脈硬化がみられ、肝臓、骨格筋、心筋などに異所性の脂肪沈着が生じることが知られる[24]。従ってPPAR-γを活性化するインスリン抵抗性改善薬は糖尿病に対する追加治療薬として使用されるのみならず、内臓脂肪の蓄積や異所性の脂肪沈着に対する改善効果も期待され[11]、さらに心保護作用も一部の臨床試験で報告されている[25-26]。同様の効果が期待されているのはインクレチン関連薬である。インクレチンは食事で小腸から分泌される消化管ホルモンで、膵β細胞におけるインスリン分泌促進作用と膵α細胞におけるグルカゴン分泌抑制作用を示す。インクレチン関連薬にはジペプチジルペプチダーゼ(DPP)-4阻害薬（内服薬）とグルカゴン様ペプチド(GLP)-1受容体作動薬（注射薬）があり、今日糖尿病の臨床では広く使用されている。これらの薬剤は心筋細胞に対する保護作用や心収縮力の改善作用により虚血性ならびに非虚血性の心不全に対する治療効果が期待されている[27]。図2にGLP-1のさまざまな臓器に対する生理作用を示す。これらインスリン抵抗性改善薬やインクレチン関連薬の心保護効果はインスリン抵抗性の改善により心筋本来のmetabolic switchの機能が正常化し、心筋の基質選択性が回復するために心機能が改善することを示しており、今後の心不全における追加治療薬として期待される。

おわりに

既知の特発性心筋症の多くはインスリン抵抗性を有しており、またインスリン抵抗性がそれらの病態や予後に深く関与している。またインスリン抵抗性はそれ自体が心筋のmetabolic switchを変調させ、エネルギー基質の選択性を阻害し、異所性脂肪沈着を来たして心筋障害や心不全を招くことを述べた。わが国におけるインスリン抵抗性の蔓延によりインスリン抵抗性心筋症は今後心不全の早期ステージの原因疾患として認識されるべきである。しかし一方でインスリン抵抗性改善薬やインクレチン関連薬などがインスリン抵抗性心筋症に対する新たな治療薬として期待されている。インスリン分泌予備能が低い日本人におけるインスリン抵抗性心筋症のさらなる病態解明と早急な対策が望まれる。

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－研究資料－

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成人先天性心疾患における健康指標
―心室中隔欠損症とファロー四徴症の比較―

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Health-Related Parameters in Adults with Congenital Heart Diseases: Comparison of Ventricular Septal Defect and Tetralogy of Fallot

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Abstract

Adult congenital heart disease is currently prevalent due to improved procedures of open heart surgery and perioperative intensive care. The present study aimed to investigate the health-related parameters in adult patients with ventricular septal defect (VSD, n = 11) and tetralogy of Fallot (TOF, n = 13), which are representatives of congenital heart diseases. Age- and sex-matched participants of health check-up program were served as controls (n = 29). Somatic growth such as body weight ($p = 0.038$) and height ($p = 0.009$) was significantly poor in the TOF group relative to the control group, whereas blood pressure was equivalent among the three groups. Fasting glucose level in the TOF group was significantly elevated than that in two other groups ($p \leq 0.001$), whereas total cholesterol level was significantly lower in the TOF group than that in the VSD group ($p = 0.030$) and the control group ($p = 0.011$). Considering fetal cyanotic stress and low cardiac output in TOF, these results were compatible with fascinating hypothesis of fetal origins of adult diseases such as diabetes.

Key Words: Adult disease, Fetal origin, Tetralogy of Fallot, Ventricular septal defect

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はじめに

先天性心疾患は出生 100 人に約ひとりの割合で発生するとされており、決して希な疾患ではない。また先天性心疾患は、その根治術式の進歩や周術期管理の向上によって、その生命予後は著しく改善し、現在その多くが成人するようになってきている[1]。

現在我が国では約40万人以上の成人先天性心疾患の大人がいて、毎年約 9,000 人の先天性心疾患の患児が成人するとされている[2]。これらを背景に大学保健管理の領域でも、成人先天性心疾患をもつ学生に遭遇する機会が近年増えつつある。

そのような現状の一方で、大学生の成人先天性心疾患の実態を把握するのは意外と困難であり、疾患の性質から本人が秘匿したり、修学や就職活動上の問題を周囲に相談できずに大学生生活が消極的になったり、自信喪失感を持つケースもある。また成人先天性心疾患では生活習慣病のリスクが通常より高いという報告も最近みられる[3]。実際に成人先天性心疾患をもつ本学の学生および卒業生を対象とした少数例でのわれわれの調査結果でも、脂質異常症、過体重、耐糖能異常など、全例何らかの生活習慣病を有していた[4]。

そこで先天性心疾患のなかで代表的な心室中隔欠損症（Ventricular Septal Defect: VSD）とファロー四徴症（Tetralogy of Fallot: TOF）に焦点を当てて、医療機関に通院中の成人例を対象として、いくつかの健康指標を健常成人と比較検討することを本研究の目的とした。

対象と方法

成人先天性心疾患をもつ本学学生および卒業生を含む国立大学法人九州大学病院に通院加療中または管理中の VSD の症例 11 名および TOF の症例 13 名を対象とした。全例修復術を幼少時に受けており、理学的に心不全を呈する例、心房細動などの不整脈を有する例、C 型慢性肝炎をもつ例、ダウン症候群など他の先天異常を合併する例は対象から除外した。また宗像医師会病院の健診センターを健康診断目的で受診した集団の中から性と年齢をマッチさせて無作為に抽出した29名を対照者とした。全例カルテベースで臨床背景、理学的所見、血液生化学検査などの実態を調査した。

統計解析は Kolmogorov-Smirnov 検定でデータ分布の正規性を検定し、正規性を示す場合は一元配置分散分析と Tukey の方法での多重比較を行った。また非正規性の場合は Kruskal-Wallis の検定を行った。なお本研究は九州大学病院メディカルインフォーメーションセンターでの病院業務関連データの抽出承認を得て行った（第 11-0134 号）。

結果

三群の症例は全例無投薬の状態で、VSD 群と TOF 群は九大病院の内科再来で定期的に経過観察をされていた。全例で特に意識的な食事療法や運動療法は行っておらず、開心術後には習慣的な薬物の服用もなかった。

健康指標に関する結果を次頁のTableに示した。データは全て平均値 ± 標準偏差であり、p値は三群間いずれかの有意差と特定の二群間の有意差を示す。VSD群、TOF群および対照群の三群間で性と年齢はマッチしており、身長はTOF群が対照群より有意に低かった（$p = 0.009$）。体重もTOF群で対照群より有意に少なかった（$p = 0.038$）。体格指数（body mass index: BMI）は三群間に有意差はなかった。また血圧値は収縮期血圧も拡張期血圧も三群間で有意差は認めなかった。

さらに血液生化学検査の結果では、空腹時血糖値と総コレステロール値で三群間に有意差を認めた。すなわち空腹時血糖の平均値はTOF群がVSD群（$p = 0.001$）や対照群（$p < 0.001$）より有意に高かった。また総コレステロール値の平均値は逆にTOF群がVSD群（$p = 0.030$）や対照群（$p = 0.011$）より有意に低かった。中性脂肪値には三群間で明らかな有意差を認めなかった。

考察

先天性心疾患は今日そのほとんどの症例が成人するようになり、内科、心臓外科、麻酔科、産科、ケースワーカー、臨床心理士、遺伝カウンセラーなどが多職種で疾患管理、デバイス管理、心理相談、遺伝相談、修学や就職の支援などに包括的に関与することが望まれている。今回の先天性心疾患を対象とした健康調査では、代表としてVSDとTOFを取り上げた。VSDは先天性心疾患の中で最も高頻度で見られる非チアノーゼ性の単純シャント疾患であり、TOFは比較的高頻度に認めるチアノーゼ性の複雑心奇形である。事実、福岡市の学校心臓検診でも小・中・高・特別支援学校の各1年生で何らかの先天性心疾患は術前・術後を含めて0.53%に認められており、内訳はVSD、心房中隔欠損症（ASD）、TOFの順に多かった[5]。

今回、先天性心疾患を持つ成人例の生活習慣病を明らかにすることを目的にその健康指標を検討した。その結果、VSD群とTOF群ともに高血圧は認めなかったが、TOF群で体格が有意に小さかった。TOFにおける修復術