Original Article

Abnormal Glucose Tolerance Contributes to the Progression of Chronic Heart Failure in Patients with Dilated Cardiomyopathy

Jiyoong KIM[1)], Satoshi NAKATANI[1)], Kazuhiko HASHIMURA[1)], Kazuo KOMAMURA[1)], Hideaki KANZAKI[1)], Masanori ASAKURA[1)], Hiroshi ASANUMA[1)], Yoshihiro KOKUBO[1)], Hitonobu TOMOIKE[1)], and Masafumi KITAKAZE[1)]

Since 1) dilated cardiomyopathy (DCM) causes chronic heart failure (CHF), and 2) augmentation of neurohumoral factors such as angiotensin II impairs glucose metabolism, we examined the rate of abnormal glucose metabolism in patients having both DCM and CHF and whether correction of the impairment of glucose metabolism would improve the pathophysiology of CHF in DCM patients. A 75-g oral glucose tolerance test (OGTT) was performed in 56 patients with DCM-induced CHF and 168 age- and sex-matched control subjects. Among the CHF patients, 26.8% and 50.0% suffered from diabetes mellitus (DM) and impaired glucose tolerance (IGT), respectively, showing that abnormal glucose tolerance was more prevalent in DCM patients than in the control subjects (7.7% and 14.3%, respectively). In the patients with DCM-induced CHF, a correlation was observed between the brain natriuretic peptide (BNP) levels and the difference between the plasma glucose levels at the time of fasting and at 2 h of OGTT. Since neither DM nor IGT are thought to cause DCM, the abnormalities of glucose metabolism may be attributed to the progression of CHF. Furthermore, we tested whether correction of the abnormal glucose tolerance using voglibose (an α-glucosidase inhibitor) would improve the severity of CHF in another group of 30 patients with DCM-induced CHF and IGT. The patients treated with voglibose for 24 weeks showed decreases in left ventricular dimension, NYHA functional classification values, and plasma BNP levels, and an improvement in cardiac function. In conclusion, abnormal glucose tolerance was more prevalent among patients with DCM-induced CHF than controls, and the correction of IGT improved the pathophysiology of CHF. (*Hypertens Res* 2006; 29: 775–782)

***Key Words*: heart failure, diabetes mellitus, impaired glucose tolerance, voglibose**

Introduction

The regimens for the treatment of patients with chronic heart failure (CHF) include angiotensin-converting enzyme (ACE) inhibitors, β-adrenergic receptor blockers, digitalis and diuretics (*1*). However, despite these medical therapies, since CHF remains one of the major causes of death or hospitalization worldwide, we need to seek a new strategy to treat CHF. CHF is characterized by impaired cardiac performance, inflammation, and neurohormonal imbalance (*2*). Indeed, increases in catecholamine, cytokine, and angiotensin II levels are thought to play important roles in the pathophysiology of CHF (*3–5*). On the other hand, catecholamines and angiotensin II have both been shown to contribute to abnormal glucose tolerance, and either transient high glucose exposure or

From the [1)]Cardiovascular Division, National Cardiovascular Center, Suita, Japan.

This work was supported by Grants-in-Aid for Human Genome, Tissue Engineering and Food Biotechnology (H13-Genome-011), Health and Labour Sciences Research Grants, and a grant from the Japan Cardiovascular Research Foundation.

Address for Reprints: Masafumi Kitakaze, M.D., Ph.D., Cardiovascular Division of Internal Medicine, National Cardiovascular Center, 5–7–1 Fujishirodai, Suita 565–8565, Japan. E-mail: kitakaze@zf6.so-net.ne.jp

Received May 12, 2006; Accepted in revised form July 5, 2006.

Table 1. Clinical Characteristics of the Control Subjects and DCM Patients

	Control	DCM	Significance
Subjects	168	56	
Age (years old)	55.2±1.1	55.2±1.2	n.s.
Sex (%male (male, female))	76.8 (129, 39)	76.8 (43, 13)	n.s.
Body weight (kg)	56.9±1.0	58.6±1.2	n.s.
Plasma BNP levels (pg/dl)	—	367.1±121.9	
%FS (%)	—	21.4±1.7	
LVDd (mm)	—	58.7±2.1	
NYHA IIs/IIm/III	—	12/29/15	
Diabetes mellitus (%)	7.7	26.8	$p<0.05$
IGT (%)	14.3	50.0	
Normal glucose metabolism (%)	78.0	23.2	
Heart rate (bpm)	71.9±0.45	72.0±0.42	n.s.
Systolic BP (mmHg)	129±0.95	128±0.89	n.s.
Diastolic BP (mmHg)	76.2±0.53	76.0±0.50	n.s.
Total cholesterol levels (mg/dl)	206±1.60	207±2.52	n.s.
Triglicelide levels (mg/dl)	120±3.30	125±6.50	n.s.
Uric acid levels (mg/dl)	5.50±0.16	5.56±0.10	n.s.
Smoking (%)	26.3	22.4	n.s.
Concomitant drugs (%)			
Digoxin		60	
Diuretics		89	
β-Blockers		70	
Angiotensin converting enzyme inhibitors		75	
Angiotensin receptor blockers		12	
Steroids		0	

DCM, dilated cardiomyopathy; BNP, brain natriuretic peptide; FS, fractional shortening; LVDd, left ventricle end-diastolic dimension; NYHA, New York Heart Association; IGT, impaired glucose tolerance; BP, blood pressure. The number in the table is the number of the subjects, mean±SEM or the percentile of the subjects.

decreased insulin sensitivity can result in cellular injury *via* the generation of oxidative stress and provocation of myocardial apoptosis (*6–11*). There are several lines of evidence showing that both high blood glucose level and insulin resistance are major risk factors for CHF (*12–18*), suggesting that either 1) the impairment of glucose metabolism is the primary cause of CHF (*19*, *20*) or 2) an impairment of glucose metabolism newly developed during the progression of CHF contributes to the worsening of CHF (*20–22*). In a clinical setting, it is difficult to determine whether or not the impairment of glucose metabolism follows the occurrence of CHF and contributes to the progression of CHF. One strategy for resolving this question would be to investigate the prevalence of the impairment of glucose metabolism in patients with CHF caused by dilated cardiomyopathy (DCM), because neither diabetes mellitus (DM) nor impaired glucose tolerance (IGT) is believed to cause primary DCM. If the prevalence of DM or IGT is higher in patients with DCM-induced CHF, we suggest the abnormalities of glucose metabolism may occur along with the progression of CHF

To test this hypothesis, we examined the prevalence of abnormalities of glucose metabolism revealed by not only fasting glucose levels but also an oral glucose tolerance test (OGTT) in patients with DCM-induced CHF. Furthermore, we tested whether administration of an α-glucosidase inhibitor (αGI) for 24 weeks would improve the severity of CHF in 30 patients with DCM-induced CHF and IGT.

Methods

Protocol I: The Prevalence of Impairment of Glucose Metabolism in DCM Patients with CHF and Normal Control Subjects

We studied 56 DCM patients with symptomatic CHF between January 2004 and January 2005. The criteria for enrollment in this study were 1) clinical diagnosis of DCM, 2) clinical evidence of CHF despite conventional therapy as quantified by a New York Heart Association (NYHA) functional classification of II to III, and 3) a left ventricular fractional shortening (FS) below 30%, as assessed by two-dimensional echocardiography. There were 43 men and 13 women with a mean age of 55.2 years. Using coronary angiography, a ventriculogram, myocardial biopsy or echocardiography, all patients were

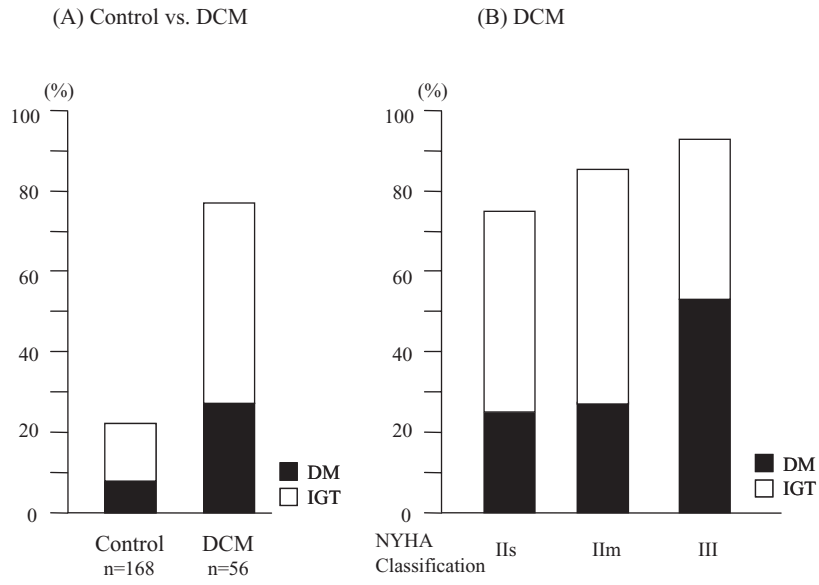

Fig. 1. *Prevalence of either impaired glucose tolerance (IGT) or diabetes mellitus (DM) in patients with DCM-induced CHF or healthy control subjects. A: The incidence of either DM or IGT in the CHF group was higher ($p < 0.001$) than in the control group. B: The DCM patients were classified according to the New York Heart Association (NYHA) classification.*

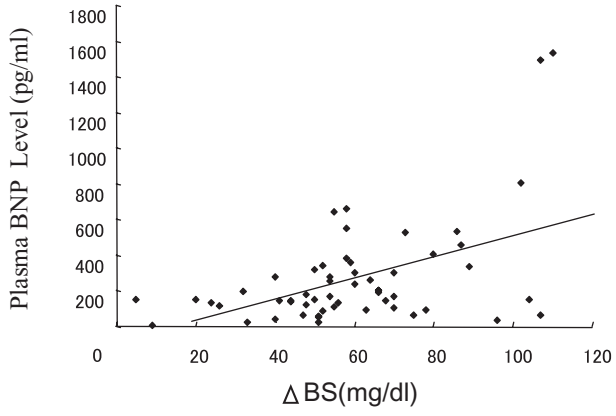

Fig. 2. *The relationship between the BNP level and the change in glucose level between fasting and 2 h after the 75-g OGTT (ΔBS). These two parameters were linked to each other (the plasma BNP level [pg/ml] = −117.0 + 6.516 ΔBS [mg/dl],* $p < 0.001$, $r^2 = 0.259$).

diagnosed as having DCM. Exclusion criteria were 1) chronic obstructive pulmonary disease, 2) either history or evidence of ischemic heart disease, 3) cerebrovascular disease, 4) peripheral vascular disease, 5) cancer, 6) estrogen replacement therapy, 7) insulin-dependent DM, 8) any disease that may secondarily cause DM, 9) the use of drugs that can induce DM, such as steroids, and 10) pregnancy. The severity of CHF was assessed by the plasma brain natriuretic peptide (BNP) levels, the echocardiographic data and the NYHA classification. BNP levels were measured using a specific immunoradiometric assay. Informed consent was obtained from each patient before participation in this study in accordance with institutionally approved protocols. As a control, we enrolled 168 age- and sex-matched subjects who had a community health examination at Suita City. Three control subjects were for each patient. Subjects with a past history of heart disease were excluded from the analysis. The fasting plasma glucose levels and the plasma glucose levels 120 min after the 75-g OGTT test were examined in all of the patients except those who had already been diagnosed with DM before entry into the study.

Protocol II: A Prospective Study to Test the Effect of Voglibose on Plasma BNP Levels and the Parameters Obtained from Echocardiography in Patients with DCM-Induced CHF and IGT

We studied 30 DCM patients with symptomatic CHF at our institute. The criteria for enrollment in this study were 1) clinical diagnosis of DCM, 2) clinical evidence of CHF despite conventional therapy, 3) the presence of abnormalities of IGT and 4) low left ventricular FS (below 30 %) as assessed by two-dimensional echocardiography. All the patients had NYHA functional classifications of II to III. DCM was diagnosed as in Protocol I. There were 17 men and 13 women with a mean age of 56 years. Exclusion criteria included chronic obstructive pulmonary disease, pregnancy, and severe liver disease, which was defined as a hepatic enzyme level more than twice the upper limit of normal. All patients were treated by optimal and stable doses of β-blockers and ACE inhibitors for at least 3 months before screening echocardiography and

Table 2. Baseline Clinical Characteristics of the CHF Patients Treated with or without Voglibose

	Control group	Voglibose group	Significance
Subjects	15	15	
Age (years old)	57.1±3.2	54.9±3.3	n.s.
Sex (male:female)	8:7	9:6	n.s.
LVDd (mm)	67.8±3.1	65.5±2.7	n.s.
FS (%)	16.3±2.1	15.8±1.7	n.s.
Heart rate (bpm)	79±2.3	84±3.3	n.s.
Systolic BP (mmHg)	112±3.3	107±3.2	n.s.
Diastolic BP (mmHg)	67.2±2.2	64.3±3.4	n.s.
Pre NYHA class (II/III)	4/11	6/9	n.s.

CHF, chronic heart failure; other abbreviations are the same as in Table 1. The number in the table is either number of the subjects or mean±SEM.

randomization. Patients were randomly divided into the groups with and without voglibose ($n=15$ for the voglibose group, and $n=15$ for the control group). The dose of voglibose was 0.3 mg just before each meal, and there were no patients who discontinued the intake of either voglibose or drugs for CHF.

The primary endpoints were a change in the NYHA functional class and a change in the plasma BNP levels. Additional analyses were performed using the echocardiogram to obtain the changes in left ventricular or atrial dimensions. A randomization was performed according to a randomization list generated by computers at the Clinical Study Support Center of Japan (Suita, Japan).

Measurements

NYHA Classification

Functional class was evaluated by certified cardiologists, according to the NYHA classification, after the clinical examinations. Heart failure was defined as NYHA class I–III at baseline. We did not enroll the patients with NYHA IV because catecholamines are administered in such patients and may modulate the glucose metabolism.

The NYHA classification of each patient was estimated by 3 independent cardiologists who did not have knowledge of the patients. If the 3 estimations did not agree, we used the median of the 3 values.

IGT and DM

In 1997, the American Diabetes Association adopted new criteria for diabetes (*23*, *24*). We followed these criteria in the present study: patients with a single fasting blood glucose level of more than 125 mg/dl were considered to have DM. In the other subjects, we performed a 75-g OGTT, and IGT was considered to be present in patients whose glucose levels at 120 min after intake of 75 g of glucose were between 140–199 mg/dl, and patients whose glucose levels were more than 199 mg/dl were also classified as having DM.

Echocardiography

Echocardiograms were performed and checked by cardiologists who had no information about the patients. Echocardiographic measurements were performed using the guidelines of the American Society of Echocardiography. Left ventricular end-diastolic and end-systolic dimensions (LVDd and LVDs, respectively), and left atrial diameter (LAD) were recorded by M-mode (SSA 260A, SSH 160A [Toshiba, Tokyo, Japan], Sonos 2000 [Hewlett Packard, CA, USA], SSD 870, or SSD 2200 [ALOKA, Tokyo, Japan]). We calculated FS (%) as $(LVDd - LVDs) \times 100/LVDd$. Fifteen technicians trained in cardiac echocardiography randomly obtained echocardiograms of all of the patients in a single echo-laboratory at our institute, and these results were verified by two cardiologists.

Plasma BNP Measurement

Blood was sampled from each patient in the sitting position in a syringe containing both EDTA (1 mg/dl) and aprotinin (103 kIU/ml). Serum was separated within 6 h and the samples were stored at −20°C until the measurements. The concentration of BNP was measured within 1 week after the plasma sampling by an immunoradiometric assay (IRMA) method (Shionoria BNP test at the SRL Laboratory, Tokyo, Japan). This test is a one-step immunoradiometric assay that uses two different monoclonal antibodies that recognize the C-terminal structure and the disulfide bond–mediated ring structure of BNP 32, respectively.

Statistical Analysis

Baseline characteristics were compared by Fisher's exact, χ^2 test or Cochran-Mantel-Haenszel test for categorical variables. ANOVA was used to test for treatment-group baseline differences for continuous variables. Within-treatment analyses of changes were performed using a Student's *t*-test, and values of $p<0.05$ were considered to indicate statistical significance (*25*).

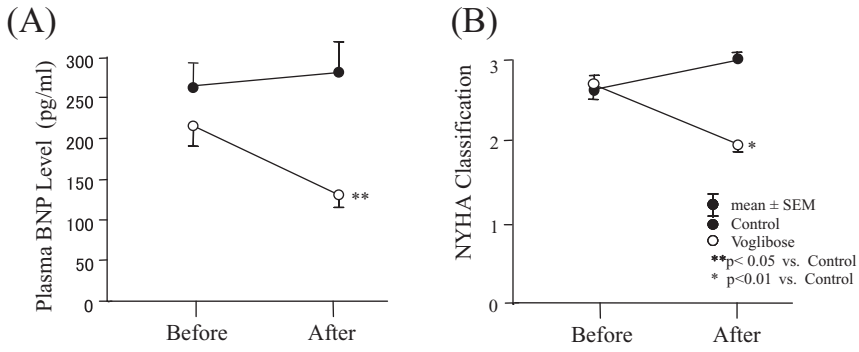

Fig. 3. *Plasma BNP level (A) and NYHA Functional classification (B) before and after the treatment with voglibose. The treatment with voglibose decreased plasma BNP level and NYHA class, but neither plasma BNP level nor NYHA class was changed in the control group.*

Results

Table 1 shows the patients' characteristics in Protocol I. Among the 56 CHF patients with symptomatic DCM, 12 patients (21%) were in NYHA class IIs, 29 patients (52%) in class IIm, and 15 patients (27%) in class III. They were treated with digitalis, diuretics, β-blockers, and/or angiotensin converting enzyme inhibitors. Twenty-six point eight percent and 50.0% of the 56 patients suffered from DM and IGT, respectively (Fig. 1A). Among the 168 control subjects, 7.7% and 14.3% suffered from DM and IGT, respectively (Fig. 1A). The incidences of both DM and IGT in the CHF group were higher ($p<0.001$) than those in the control group. Furthermore, the incidences of both DM and IGT increased as the severity of CHF assessed by NYHA classification progressed (Fig. 1B). There were no significant differences in medication for CHF, especially diuretics or β-blockers, between the patients with and those without either DM or IGT. Diuretics were used in 88% of the patients with either DM or IGT, and in 92% of the patients without either DM or IGT. β-Blockers were used in 70% of the patients with either DM or IGT, and in 69% of the patients without either DM or IGT, indicating that the use of diuretics and the use of β-blockers did not differ between patients with and those without either DM or IGT. Among the CHF patients who received a 75-g OGTT, the BNP levels were correlated with the change in glucose level between fasting and 2 h after the 75-g OGTT (ΔBS) ($n=56$, $p<0.001$, Fig. 2). We also investigated 189 CHF patients diagnosed with DCM, hypertensive heart disease and primary valvular disease and obtained the same results (data not shown).

We administered voglibose to the CHF patients due to the patients with IGT and DCM-induced CHF for 24 weeks. Table 2 shows the patients' characteristics at baseline. All patients completed the protocol, and no patients died during the 24-week study. In addition, the doses of voglibose and the other drugs for CHF were not altered during the study. Neither blood pressure nor heart rate differed between the groups with and without voglibose before the treatment (systolic blood pressure [SBP]: 107±3 *vs*. 112±3 mmHg; diastolic blood pressure [DBP]: 64±3 *vs*. 67±2 mmHg; heart rate: 84±3 *vs*. 79±2 bpm, respectively), and there were no significant changes in any of these parameters at 24 weeks after the onset of the study in either the group with or that without voglibose (SBP: 109±3 *vs*. 110±3 mmHg; DBP: 62±2 *vs*. 65±2 mmHg; heart rate: 80±2 *vs*. 82±2 bpm, respectively). The plasma BNP levels and NYHA classification significantly decreased (Fig. 3), and LVDd, LVDs and LAD significantly decreased and FS significantly increased (Fig. 4) in the patients in the voglibose group compared with the control group. This indicates that voglibose ameliorated the severity of CHF.

Discussion

The present study has demonstrated that abnormalities of glucose metabolism are tightly associated with the severity of CHF, and contribute to the deterioration of CHF in patients with DCM. Most importantly, this is the first report to show that correction of the abnormalities of glucose metabolism using αGI in patients with DCM-induced CHF and IGT improved the pathophysiology of CHF.

CHF and Abnormalities of Glucose Metabolism

Several reports have described a relationship between abnormalities of glucose metabolism and the progression of CHF, and have suggested that abnormalities of glucose metabolism contribute to the pathophysiology of CHF (*12–17*). Several investigations have shown that DM, and even relatively mild glucose abnormalities, are strongly associated with cardiovascular morbidity and mortality (*26–28*), indicating that DM is an independent risk factor for CHF (*18–23*). However, the opposite may also be true, as was suggested in the present study, *i.e.*, the fact that both DM and IGT may themselves be

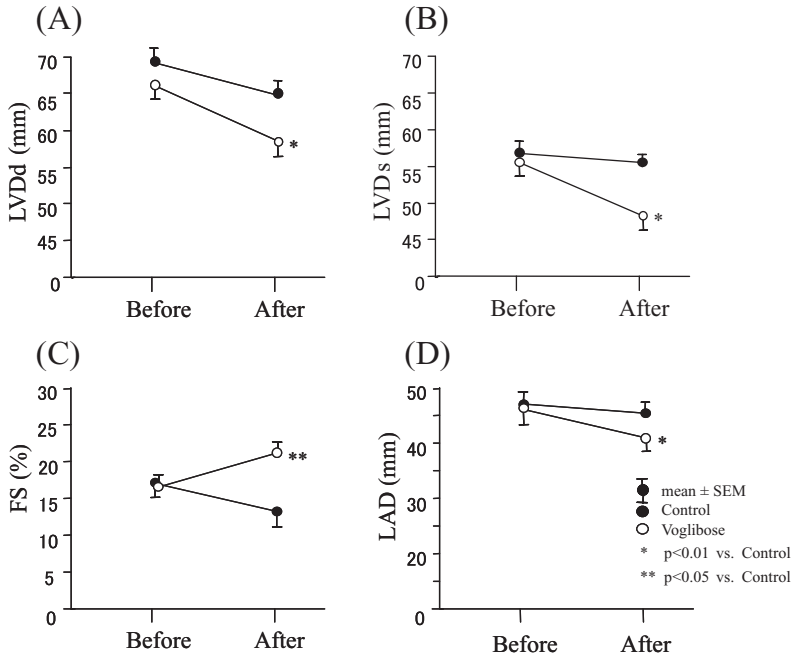

Fig. 4. *Changes in left ventricular end-diastolic volume (LVDd) (A) or end-systolic volume (LVDs) (B), LV fractional shortening (FS) (C) and left atrial diameter (LAD) (D) before and after the treatment for 24 weeks in the voglibose groups. These parameters were not changed in the control group.*

caused by CHF. Since 1) we enrolled patients with DCM-induced CHF, and 2) neither DM nor IGT seems to cause DCM, the abnormalities of glucose metabolism may not necessarily precede the incidence of CHF. Rather, the abnormalities of glucose metabolism may occur along with the progression of CHF, which is a major hypothesis of the present study. There is a report that CHF was associated with the subsequent development of non–insulin-dependent diabetes mellitus (NIDDM) in a group of elderly subjects (*21*), and the present study of the frequent prevalence of abnormalities of glucose metabolism in DCM patients with CHF also supports the present hypothesis. Intriguingly, in addition to the results of Amato *et al*. (*21*), we further observed that IGT is also tightly involved in the pathophysiology of CHF. This is confirmed by the relationship between the severity of either IGT or DM and CHF, and the results of voglibose-induced improvements of CHF shown in the present study.

Possible Mechanisms by Which CHF Causes Abnormal Glucose Tolerance

CHF is known to be an insulin-resistant state that may constitute one of the major risk factors for the development of NIDDM (*13*, *14*, *16*, *20*). Advanced CHF leads to progression of insulin resistance, characterized by fasting and stimulated hyperinsulinemia (*14*), which is a major risk factor for the development of DM (*29*).

There are several possible mechanisms by which CHF may trigger either IGT or DM. First, since either β-blockers or diuretics, which may cause either DM or IGT, are used in CHF patients, these drugs may induce either IGT or DM. However, this was not the case in the present study, because these drugs were equally used in CHF patients with or without abnormal glucose tolerance. Secondly, patients with CHF often show reduced physical activity, which may increase the risk of IGT or DM (*30*). Either insulin resistance or reduced physical activity, or both, may therefore explain the increased risk of abnormal glucose tolerance in patients with CHF. The third possibility is the contribution of free fatty acids (FFA); catecholamines, which are elevated as the pathophysiology of CHF progresses, increase the FFA levels in the adipose tissue, and the elevated FFA levels increase the expression levels of mitochondrial uncoupling proteins and decrease the expression of GLUT4, which promotes the uptake of glucose (*31*). The fourth possibility is that angiotensin II is involved. Angiotensin II, which is elevated in patients with CHF, decreases the insulin sensitivity and impairs the β cells of the pancreas (*32*). The fifth possibility is that BNP, which is also elevated in patients with CHF, played a role in the present results. However, this possibility is less likely because BNP increases adiponectin, which may improve the glucose tolerance. Any one of these factors, or several in combination, may be the cause of the abnormalities of glucose metabolism.

Cellular Mechanisms by Which Abnormal Glucose Abnormality Ameliorates CHF

High glucose exposure, even for a short length of time, produces oxidative stress, and provokes cellular damages such as necrosis or apoptosis (*8–11*). If this occurs in cardiomyocytes, myocardial dysfunction may be worsened by DM or even IGT. Indeed, postprandial hyperglycemia is an indicator of myocardial perfusion defects in DM patients (*33*). Secondly, insulin resistance that causes energy depletion of the myocardium may provoke cardiac dysfunction. Thirdly, the abnormalities of glucose metabolism cause the impairments of endothelial cells attached to cardiomyocytes, and the endothelial dysfunction may be involved in the deterioration of CHF. This is because NO is known to be beneficial for cardiomyocytes as well as smooth muscle cells (*34*), and we have previously reported that depletion of NO causes cardiac hypertrophy or coronary insufficiency *via* activation of angiotensin II followed by the activation of either ERK or P70 S6 kinase (*35*). Indeed, Hirooka *et al*. reported that endothelial function and angiotensin II compete with each other (*36*).

Clinical Impact of the Present Observations

The present study should have an impact on the treatment of CHF. If, in fact, the prevalence of abnormal glucose tolerance is very high among CHF patients worldwide, voglibose may become a novel therapy for the treatment of patients with CHF and abnormal glucose metabolism. Furthermore, if either transient high glucose exposure or decreased insulin sensitivity makes the failing myocardium worse, voglibose may improve the severity of CHF. Further investigations will be needed to examine this point.

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