

## Effects of sulfonylureas on left ventricular mass in type 2 diabetic patients

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**Lee T-M, Lin M-S, Tsai C-H, Huang C-L, Chang N-C.** Effects of sulfonylureas on left ventricular mass in type 2 diabetic patients. *Am J Physiol Heart Circ Physiol* 292: H608–H613, 2007. First published August 25, 2006; doi:10.1152/ajpheart.00516.2006.—Myocardial ATP-sensitive potassium ( $K_{ATP}$ ) channels have been implicated in attenuating cardiac hypertrophy by modulating endothelin-1 concentrations. Sulfonylureas differ in their affinity for cardiac  $K_{ATP}$  channels and therefore may vary in their effects on left ventricular (LV) mass. We sought to determine the differential effects of sulfonylureas on LV mass in type 2 diabetic patients. All patients had been taking glibenclamide for more than 3 mo before being randomized to either switch to an equipotent dose of gliclazide or continue glibenclamide. A total of consecutive 240 diabetic patients were randomized into glibenclamide, gliclazide, a combination of glibenclamide and nicorandil, or gliclazide and nicorandil for 6 mo. In the gliclazide-treated group, the LV mass index was significantly decreased compared with that in the glibenclamide-treated groups. Nicorandil administration significantly reduced LV mass in glibenclamide-treated patients compared with patients treated with glibenclamide alone. Measurements of endothelin-1 concentrations mirrored the functional status of  $K_{ATP}$  channel. Multivariate analysis revealed that regression of LV mass was significantly correlated only with the changes in endothelin-1 ( $P < 0.0001$ ). Our results show that  $K_{ATP}$  channels may play a pathogenetic role, probably through an endothelin-1-dependent pathway, in diabetes mellitus-related ventricular hypertrophy. Patients treated with gliclazide may have a beneficial effect in attenuating ventricular mass.

adenosine 5'-triphosphate-sensitive potassium channels; diabetes mellitus; glibenclamide; gliclazide; ventricular hypertrophy

INCREASED LEFT VENTRICULAR (LV) mass is a risk factor of cardiac morbidity and mortality not only in patients with essential hypertension but also in the general population (27). The risk increase is independent of other cardiovascular risk factors, including hypertension (7). Previous data revealed that LV mass regression reduced cardiovascular complications (27). Thus LV mass reduction is widely accepted as a desirable treatment goal.

Cardiac hypertrophy is a complex process involving numerous signaling pathways. Pharmacological therapies, such as angiotensin-converting enzyme inhibitors and  $\beta$ -blockers, have been used to improve cardiac hypertrophy (28). Previous studies have shown that LV remodeling, a process of ventricular hypertrophy, is improved by nicorandil treatment after myocardial infarction (26), implying that myocardial ATP-sensitive potassium ( $K_{ATP}$ ) channels may play a role in ventricular hypertrophy. Recently, our group (18) showed a direct

relation between the activation of myocardial  $K_{ATP}$  channels and ventricular remodeling by administering  $K_{ATP}$  channel antagonists in hyperlipidemic rabbits. Activation of  $K_{ATP}$  channels has been shown to attenuate cardiac hypertrophy by inhibition of endothelin-1 (ET-1) (33), a key mediator of protein synthesis for hypertrophic changes.

Previous studies have shown that diabetic patients have a substantially higher LV mass index than nondiabetic patients (6). The mechanisms involved remain unclear. Sulfonylureas represent the most commonly prescribed pharmacological treatment for type 2 diabetic patients. Sulfonylurea drugs stimulate insulin secretion by closing  $K_{ATP}$  channels in pancreatic  $\beta$ -cell membrane. Unfortunately,  $K_{ATP}$  channels also occur in the cardiovascular system, where they are thought to play an important role in LV hypertrophy. Thus the use of sulfonylurea drugs may be harmful. Differential response of sulfonylurea drugs was determined using the sulfonylurea receptor (SUR) isoform because multiple regions of SUR contribute to coupling antagonist-occupied site(s) with the inwardly rectifying potassium channel ( $K_{IR}$ ) gating machinery (3). Gliclazide is pharmacologically distinct from glibenclamide because of differences in SUR receptor-binding properties (9) that could result in a reduced binding to cardiomyocyte  $K_{ATP}$  channels as reflected in the lower  $K_{ATP}$  channel current inhibition activity (16). Gliclazide is a sulfonylurea with high affinity and strong selectivity for pancreatic SUR 1 but has no significant action on cardiac SUR 2A (9).

To our knowledge, no studies have assessed whether therapeutic doses of sulfonylureas in diabetic patients may modulate LV mass. The goal of the present study was to determine whether the chronic use of sulfonylurea drugs alters ventricular mass and to assess whether an agonist of  $K_{ATP}$  channels, nicorandil, can mimic the beneficial effects of attenuated ventricular hypertrophy in diabetic patients.

### METHODS

**Subjects.** The study was conducted prospectively. The protocol consisted of a 4-wk screening period and a 6-mo treatment period (Fig. 1). Patients ages 40–80 yr were eligible if they met the National Diabetes Data Group definition for type 2 diabetes, with endogenous insulin production (fasting C-peptide concentration  $\geq 0.8$  ng/ml at screening) and with glibenclamide as one of the hypoglycemic regimen. Individuals with impaired glucose tolerance were not considered in this study. Impaired glucose tolerance is determined by measuring plasma glucose levels 2 h after glucose loading in the oral glucose tolerance test. Impaired glucose tolerance is associated with increased

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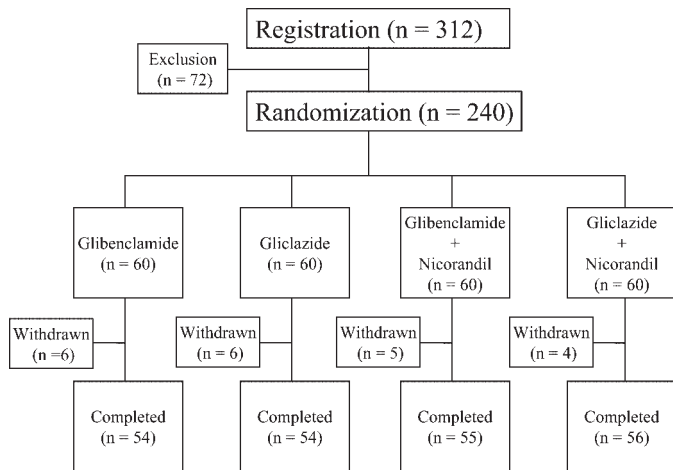


Fig. 1. Randomization protocol. For exclusion criteria, see text.

risk of developing type 2 diabetes. To date, several clinical trials have found that life style modification is the most efficacious strategy to prevent progression to type 2 diabetes. Alternative treatments include pharmacotherapy with metformin or acarbose, both of which have been demonstrated to decrease the development of type 2 diabetes (25). Other drugs, such as those indicated to treat other parameters of the metabolic syndrome, also may be useful. Because glibenclamide is not recommended for patients with impaired glucose tolerance, such patients were excluded from the study. All patients were on stable doses of oral hypoglycemic agents and other medications for at least 3 mo before undergoing screening echocardiography and randomization.

Patients were excluded from participation if they had clinical significant renal disease with plasma creatinine level  $>1.8$  mg/dl, severe valvular heart disease, atrial fibrillation, uncontrolled blood pressure  $>180/110$  mmHg, or symptoms or signs or history of cardiovascular disease. Patients with a definite indication for long-term insulin therapy were not eligible for inclusion. We defined the patients as having a definite indication for long-term insulin therapy if the glycosated hemoglobin ( $HbA_{1c}$ ) was  $>9.5\%$  on dual therapy including glibenclamide at a maximal dose of 20 mg, which was modified from a previous definition (29). Whereas patients taking angiotensin converting enzyme inhibitors, angiotensin II receptors antagonists, and lipid-lowering agents were not excluded from the study, doses were not to be changed during the study unless deemed medically appropriate.

During a 4-wk run-in period, we confirmed whether the patients were eligible for the study. Exclusion criteria were rechecked during the run-in period. Eligible patients were randomly assigned to keep original glibenclamide or to shift to gliclazide, which was titrated at the discretion of the investigator and held constant for the duration of the study period. We encouraged the investigators to achieve the goal of the American Diabetes Association's recommended targets for glycemic control including a preprandial blood glucose level of 80–120 mg/dl, a bedtime blood glucose level of 100–140 mg/dl, and an  $HbA_{1c}$  level of  $<7\%$  (2). Five milligrams of glibenclamide are equivalent to 80 mg of gliclazide in terms of glycemic control. To further confirm whether activation of  $K_{ATP}$  channels is mandatory for LV mass, we assessed diabetic patients treated with nicorandil. Nicorandil was orally administered at a dose of 15 mg/day, which has been shown to activate  $K_{ATP}$  channels (22). Consecutive patients were enrolled and randomized into four treatment groups: those treated with glibenclamide, those treated with gliclazide, those treated with glibenclamide and nicorandil, and those treated with gliclazide and nicorandil (Fig. 1). Weight and height were measured using standard techniques. Body mass index was calculated as body weight divided

by height squared. Hypertension was considered present when arterial blood pressure was persistently 140/90 mmHg or when patients received blood pressure-lowering drugs. More detailed information concerning the population studied is given in Table 1. Patients gave written informed consent to participate in this study, which was approved by the institutional ethics committee.

**Echocardiographic assessment.** Echocardiographic determinations were carried out by experienced investigators (N.-C. Chang, T.-M. Lee) blinded to clinical and laboratory data. The primary study end point was the change in LV mass index between baseline and 6 mo of therapy. In addition, the study assessed changes from baseline to the end of the study (6 mo) in LV systolic function. Study patients received two-dimensional echocardiography by a single examination at baseline and at 6-mo follow-up, respectively. A commercially available system (Hewlett-Packard Sonos 5500, Andover, MA) was used. Heart rate was determined from a continuous electrocardiographic tracing. Baseline heart rate and systemic arterial pressure were measured. The LV end-diastolic dimension (EDD), end-systolic dimension (ESD), ventricular septum thickness (VS), posterior wall thickness (PW), and LV ejection fraction were measured as described previously (19). Echocardiographic LV mass was determined using the corrected formula proposed by Penn (5):

$$\text{LV mass (in grams)} = 1.04 \times [(\text{EDD} + \text{VS} + \text{PW})^3 - \text{EDD}^3] - 13.6.$$

LV mass was indexed by body surface area ( $\text{g}/\text{m}^2$ ). Measurements were averaged for three consecutive beats. Video images were recorded for off-line analysis.

**Biochemical analysis.** Blood samples were taken after an 8-h overnight fasting at baseline and after 6 mo of treatment. It has been shown that activation of  $K_{ATP}$  channels is associated with attenuated ET-1 concentrations (33). To confirm the downstream pathways of  $K_{ATP}$  channel, we collected plasma samples for ET-1 measurements and extracted as previously described (20). Samples were immediately centrifuges at 3,000 g for 10 min, and the plasmas were stored at  $-70^\circ\text{C}$  until further analysis. ET-1 was measured by immunoassay (R&D System, Minneapolis, MN). The detection limit was 1 pg/ml for

Table 1. Clinical characteristics and lipid profiles of diabetic patients and control subjects

	Glib	Glic	Glib + Nic	Glic + Nic
<i>n</i>	54	54	55	56
M/F	32/22	30/24	34/21	32/24
Age, yr	64 ± 9	63 ± 9	64 ± 9	65 ± 10
Diabetic duration, yr	11 ± 7	11 ± 8	11 ± 9	11 ± 7
Hypertension, %	44 (81)	40 (74)	46 (84)	39 (70)
Lipid profiles				
Cholesterol, mg/dl				
Total	202 ± 35	204 ± 43	204 ± 52	213 ± 49
HDL	50 ± 12	47 ± 12	47 ± 9	47 ± 10
LDL	110 ± 36	118 ± 42	109 ± 48	119 ± 45
Triglyceride, mg/dl	212 ± 159	195 ± 126	245 ± 183	231 ± 149
Diabetic treatment				
Metformin	41	39	37	42
Acarbose	26	30	27	30
Rosiglitazone	22	22	19	20
Other treatment				
ACE inhibitors	4	3	3	2
ARB	39	32	37	35
Beta blockers	22	27	24	24
Calcium blockers	25	26	28	29
Diuretics	15	24	23	22
Statins	32	34	29	30

Values are means ± SD. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; Glib, glibenclamide; Glic, gliclazide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Nic, nicorandil.

Table 2. Hemodynamics, blood glucose, insulin, C-peptide, and BMI at baseline and 6 mo of therapy

	Glib		Glic		Glib + Nic		Glic + Nic	
	Before	After	Before	After	Before	After	Before	After
Blood pressure, mmHg								
Systolic	148±18	147±16	145±17	144±15	143±16	139±14	146±18	145±17
Diastolic	81±9	81±7	81±9	82±7	80±10	81±8	82±13	82±11
Pulse pressure	66±16	67±15	63±16	62±15	63±14	59±11	64±17	63±18
Heart rate, beats/min	76±8	76±8	75±10	76±9	76±9	75±9	76±10	77±8
HbA <sub>1c</sub> , %	8.6±1.9	8.7±1.4	8.3±1.6	8.4±1.5	8.3±2.1	8.0±1.7	8.2±1.5	8.2±1.6
Fasting plasma glucose, mg/dl	189±61	197±50	191±57	195±38	183±59	179±52	192±59	185±52
Fasting plasma insulin, mU/l	26.2±2.1	26.5±2.0	26.2±2.1	27.5±2.8	26.9±2.9	27.2±2.5	27.0±2.7	27.3±2.1
C-peptide, ng/ml	2.6±0.8	2.5±1.1	2.2±1.2	2.3±1.4	2.3±0.7	2.5±1.0	2.3±1.2	2.2±0.9
BMI, kg/m <sup>2</sup>	26.2±3.7	26.2±3.4	26.6±3.8	26.5±3.5	26.6±3.0	26.5±3.1	26.8±2.9	26.8±3.0

Values are means ± SD. BMI, body mass index; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

ET-1. There was <1% cross-reactivity with big-endothelin 22–38. Intra-assay and interassay coefficients of variation were 4.5 and 6.6%, respectively.

Fasting plasma glucose, HbA<sub>1c</sub>, insulin, C-peptide, and creatinine constituted the glycemic laboratory parameters. Plasma concentrations of total, high-density lipoprotein cholesterol, and triglycerides were measured using enzymatic methods as previously described (1, 23). Low-density lipoprotein cholesterol was calculated using the Friedewald equation (32). All blood specimens were collected at the participating sites and shipped to the central laboratory. Analyses were duplicated at a single time point, and results are expressed as mean values.

**Reproducibility of echocardiographic measurements.** To check interobserver variability of LV mass, independent and duplicate determinations were made by a second experienced investigator (T.-M. Lee) on a subgroup of 50 echocardiograms. The coefficient of variability was calculated with the formula:  $\delta = \sum (X_1 - X_2)^2 / (2n - 1)$ . The coefficient of variability ( $\delta$ /LV mass) was 0.9% (1.6 g) for duplicate LV mass measurements and 1.2% (1.1 g/m<sup>2</sup>) for LV mass index. The coefficient of variability in intraobserver variability obtained by randomly inserting 30 echocardiograms was 0.7% (1.3 g) for LV mass and 0.8% (0.8 g/m<sup>2</sup>) for LV mass index.

**Statistical analysis.** All data were analyzed using Excel (Microsoft, Seattle, WA) software loaded with SPSS software (SPSS, Chicago, IL). The continuous variables were expressed as means ± SD. Differences in baseline characteristics, hemodynamics variables, and LV mass among groups were determined by ANOVA. Baseline and 6-mo follow-up data were analyzed using the paired Student's *t*-test. For the identification of independent predictors of LV mass index, the change in LV mass index was used as the dependent variable, with changes in pulse pressure, age, and ET-1 as potential independent variables. Relationships among the changes were studied using Spearman correlation and multiple linear regression analysis. All study outcomes were analyzed only in patients who completed the 6-mo trial. A two-way ANOVA was used to search for possible effects of

nicorandil and glibenclamide on the measurements of LV mass, and if an *F* value was found to be significant, a two-tailed Student's *t*-test for paired observation with Bonferroni's correction was used to test differences. For the categorical parameters, the differences were compared by  $\chi^2$  test and Fisher's exact test if case number was <5. A *P* value <0.05 was considered statistically significant.

## RESULTS

A total of 312 patients met the criteria for inclusion, and 72 of these patients (23%) met one or more criteria for exclusion. A total of 240 consecutive patients were randomized into four study groups. There were a total of 219 evaluable and completed patients. Table 1 presents the baseline and demographic characteristics of patients in each group. There were no significant differences at baseline among the groups. Blood glucose and blood pressure were similar among the four diabetic groups throughout the study (Table 2). The effects of glibenclamide and gliclazide on insulin secretion were very similar in patients with type 2 diabetes, consistent with previous studies (31).

**Echocardiographic measurements.** At baseline, all groups had similar LV mass. After 6 mo, there was no significant change in LV mass index in the glibenclamide group (Table 3). In contrast to glibenclamide treatment, gliclazide had a significantly attenuated LV mass index (17%, *P* < 0.0001) during the follow-up compared with baseline despite an equivalent control in glycemia. There was a significantly higher LV mass index between the glibenclamide- and the gliclazide-treated groups (142 ± 38 vs. 106 ± 24 g/m<sup>2</sup> in the gliclazide group, *P* < 0.0001) after 6 mo. The reduction of LV mass index was due to reduction of LV ESD (28.1 ± 4.5 mm at baseline vs. 27.0 ± 4.4 mm at 6 mo, *P* = 0.0001) and LV EDD (43.6 ± 4.3

Table 3. Echocardiographic parameters and ET-1 levels at baseline and 6 mo of therapy

	Glib		Glic		Glib + Nic		Glic + Nic	
	Before	After	Before	After	Before	After	Before	After
LV mass, g	222±62	245±63	219±43	180±41*†	224±53	180±52*†	219±50	184±38*†
LV mass index, g/m <sup>2</sup>	128±36	142±38	129±28	106±24*†	128±28	103±28*†	125±28	105±21*†
End-systolic dimension, mm	28.2±5.1	29.1±4.9	28.1±4.5	27.0±4.4*†	28.9±6.0	27.7±5.4*	29.1±4.9	27.4±4.3*
End-diastolic dimension, mm	43.4±4.6	44.6±4.3	43.6±4.3	42.2±4.6*†	44.2±5.0	42.0±5.3*†	44.0±4.7	42.3±4.1*†
Ejection fraction, %	72±10	71±11	73±9	72±10	71±11	70±12	70±10	72±10
ET-1, pg/ml	6.1±3.2	6.6±3.4	6.3±2.4	5.7±2.9*	6.6±2.6	5.6±2.1*	6.2±2.7	5.4±2.4*†

Values are means ± SD. LV, left ventricular; ET-1, endothelin-1. \**P* < 0.05 compared with respective baseline. †*P* < 0.05 compared with the Glib group after treatment.

mm at baseline vs.  $42.2 \pm 4.6$  mm at 6 mo,  $P < 0.0001$ ). Nicorandil administration significantly attenuated LV mass index in the glibenclamide group compared with treatment with glibenclamide alone. There was no significant difference of LV mass index regression during the follow-up in groups treated with either gliclazide or gliclazide plus nicorandil ( $17 \pm 14$  vs.  $15 \pm 12\%$ ,  $P =$  not significant).

**ET-1.** There were similar baseline ET-1 levels among the four groups (Table 3). ET-1 levels were significantly reduced in gliclazide-treated patients compared with those in glibenclamide-treated patients, whose ET-1 levels remained stable throughout the study. Patients with additional nicorandil in treatment had a significant reduction of ET-1 compared with those treated with glibenclamide alone.

**Correlation.** Multiple linear regression models were assessed for each dependent variable listed in Table 4. A robust inverse correlation was found between the changes of ET-1 and LV mass index [change in LV mass index (%) =  $0.63 \times$  change in ET-1 (%) + 0.29,  $r = 0.50$ ,  $P < 0.0001$ , Fig. 2], suggesting that LV mass index increases as the severity of ET-1 increases.

To identify determinants of decrease in LV mass index, we implemented multivariate analysis (Table 5). Multivariate regression analysis was performed with LV mass index as dependent variable and age, changes in hemodynamics, and ET-1 as independent variables. The ET-1 was a factor that was significantly related to long-term improvement in LV mass index ( $\beta = 0.495$ ,  $P < 0.0001$ , adjusted  $R^2 = 0.253$ ).

## DISCUSSION

This study showed for the first time that the use of sulfonylurea drugs has effects on ventricular mass, which was associated with an ET-1-dependent pathway. Compared with glibenclamide, a significant decrease in LV mass index was observed in the gliclazide group after 6 mo of treatment. We found differences among classes of sulfonylureas on LV mass that made grouping as a homogeneous class inappropriate without stratifying on the basis of blocking cardiac  $K_{ATP}$  channels.

Our conclusions are supported by the following observations. 1) Gliclazide was associated with an attenuated LV mass index, which was not observed with glibenclamide. Relieving cardiac  $K_{ATP}$  channel blockade by shifting glibenclamide to

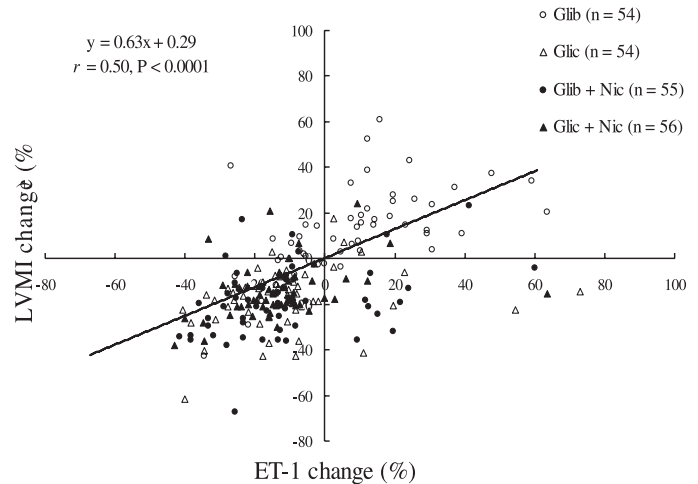


Fig. 2. Correlation of the change (%) between left ventricular mass index (LVMI) and endothelin-1 (ET-1) in the diabetic patients ( $r = 0.50$ ,  $P < 0.0001$ ,  $n = 219$ ). A greater increase of ET-1 release was associated with a greater increase of LVMI. Glib, glibenclamide; Glic, gliclazide; Nic, nicorandil.

gliclazide causes significant attenuation of LV mass, which suggested a basal modulation of LV mass by cardiac  $K_{ATP}$  channels. The effect of glibenclamide on LV mass was improved by treatment with nicorandil, further confirming the predominant role of  $K_{ATP}$  channels in this phenomenon. The observation was consistent with previous findings showing glibenclamide with much less tissue selectivity, because it blocks  $K_{ATP}$  channel in  $\beta$ -cells and cardiac muscle (9, 16). Our data are compatible with previous studies by our group showing a pathogenetic role of  $K_{ATP}$  channels in ventricular hypertrophy induced by hypercholesterolemia (18).

2) The beneficial effects of gliclazide on attenuated LV mass might be associated with reduced ET-1 levels independent of glycemic changes. Patients in whom nicorandil was coadministered had significant reductions of ET-1 compared with those treated with glibenclamide alone. Our findings were consistent with those of Xue et al. (34), showing that chronic treatment with a  $K_{ATP}$  channel agonist (iptakalim) reduces circulation ET-1 concentrations. Furthermore, this result was consistent with the notion that activation of  $K_{ATP}$  channels attenuated cardiac hypertrophy by inhibition of ET-1 (33).

In this study, we demonstrated a significant reduction of LV mass in gliclazide-treated diabetic hearts. The mechanisms by which gliclazide affected LV mass remained undefined. However, several factors can be excluded. 1) Hemodynamics: drugs neither exerted hemodynamic effects nor were associated with a change in body weight. Although nicorandil is a vasodilator,

Table 4. Correlates of percentage differences in LV mass index

Factors	Correlation Coefficient
Age	0.14
DM duration (yr)	-0.0003
$\Delta$ Systolic blood pressure	0.37
$\Delta$ Pulse pressure	0.17
$\Delta$ Fasting glucose	0.36
$\Delta$ HbA <sub>1c</sub>	0.07
$\Delta$ Insulin	0.12
$\Delta$ Body mass index	0.18
$\Delta$ LV end-diastolic dimension	0.43*
$\Delta$ LV end-systolic dimension	0.75*
$\Delta$ LV interventricular septal thickness	1.10*
$\Delta$ LV posterior wall	0.92*
$\Delta$ ET-1	0.63*

\* $P < 0.05$ .

Table 5. Multivariate analysis of independent factors for LV mass index

Factors	Standardized $\beta$ -Coefficient	95% CI	P Value
Age (per additional yr)	0.046	-0.152-0.349	0.439
Pulse pressure change (per additional %)	0.084	-0.046-0.283	0.158
ET-1 change (per additional %)	0.495	0.303-0.488	<0.0001

CI, confidence interval.

the beneficial effect of nicorandil was achieved without clinically important changes in heart rate or blood pressure. The result was consistent with the IONA results, showing that no decrease in blood pressure was observed when the chronic use of nicorandil was administered at the dose of 20–40 mg/day (12).

2) Differences in insulin concentrations: although increased insulin levels have been shown to increase LV mass (11), the insulin levels cannot be a confounding factor of LV mass. There were similar insulin levels among the four groups throughout the study.

3) Differences in glucose concentrations: LV hypertrophy might develop in diabetic patients as a result of higher glucose levels, which independently stimulated LV growth (24). However, when nicorandil was administered in diabetic patients, the LV mass improved without significant changes in blood glucose levels, suggesting that factors other than glucose might contribute to the pathogenesis of LV mass reduction in diabetic patients. Our results were consistent with previous findings of Hata et al. (10), showing that nicorandil administration did not worsen glucose control in diabetic patients.

*Other mechanisms.* The present study suggests that the mechanisms of gliclazide-induced cardioprotection may be related to nonblockade of myocardial  $K_{ATP}$  channels; however, based on the correlation shown in Table 5, ET-1 levels explain only 25% of the variation in LV mass. Therefore, gliclazide-induced attenuated LV mass cannot be attributed solely to  $K_{ATP}$  channel-related ET-1 levels, which stresses the importance of other factors. First, increased production of free radicals may induce cardiac hypertrophy via activation of mitogen-activated protein kinases (30). Blockade of free radicals alleviated the development of cardiac hypertrophy (30). The ability of gliclazide to lower oxidative stress in diabetic patients is not shared by glibenclamide (14). The antioxidant effects of gliclazide may attenuate ventricular mass. Furthermore, nicorandil possesses anti-free radical characteristics, since the nicotinamide moiety of its molecular structure is a known hydroxyl radical scavenger and an inhibitory effect on superoxide anion production (21). Thus the groups treated with nicorandil may attenuate ventricular mass by its antioxidant action. Second, blunting by nicorandil of antihypertrophic effect also may result from an increase of nitric oxide activity. The additional effect of nicorandil on top of glibenclamide could be mediated by its nitric oxide donor activity. Because glibenclamide blocks the  $K_{ATP}$  channel opening properties of nicorandil in vitro (13) without affecting its nitric oxide properties, this additional action of nicorandil on ventricular mass should be considered as a possible explanation for its beneficial effect in glibenclamide-treated patients. However, the significant correlation was observed between ventricular mass and ET-1, implying a pivotal role of  $K_{ATP}$  channel-related ET-1 in this phenomenon.

*Clinical implication.* Our results are consistent with our previous studies showing that impairment of myocardial  $K_{ATP}$  channels is associated with ventricular hypertrophy (34). Our findings have identified  $K_{ATP}$  channel as a suitable antihypertrophic strategy, particularly in the diabetic myocardium, where  $K_{ATP}$  channel-dependent mechanisms are impaired by the use of sulfonylureas. Changes in the  $K_{ATP}$  channel abundance have provided the scenario of treating the diabetic

myocardium with the  $K_{ATP}$  channel openers described in this study.

The extent to which sulfonylureas contribute to the increased risk for cardiovascular disease in diabetes has been debated, partly because sulfonylureas are not a homogeneous group of drugs in terms of their tissue specificity and their effects on cardiac structure. Our results reflect different effects of glibenclamide and gliclazide treatment on LV mass in type 2 diabetic patients. Like ischemic animals, diabetics seem to be much more cardiovascularly sensitive to sulfonylureas (17). Blockade of myocardial  $K_{ATP}$  channels with glibenclamide at therapeutic doses is associated with impaired reduction of LV mass, thereby contributing to increased mortality. It seems likely that the high selectivity for pancreatic  $\beta$ -cell  $K_{ATP}$  channels over those of cardiovascular tissues is a desirable property for sulfonylureas to be used in type 2 diabetes. Our current data add a further piece of information toward explaining the mechanisms underlying this benefit of gliclazide.

*Study limitations.* There are some limitations in the present study that have to be acknowledged. First, the reliability of echocardiographic measurement of LV mass is substantially important. Gottdiener et al. (8) have shown that the temporal variability of echocardiography for measurement of LV mass precludes its use to measure changes in mass of the magnitude likely to occur with therapy. However, our results have demonstrated an acceptable reliability of repeated measurements of LV mass for identification of clear-cut LV mass in terms of inter- and intra-observer variability. Indeed, our results were compatible with the findings of de Simone et al. (4), showing that M-mode echocardiographic measurement of LV mass demonstrated an acceptable reproducibility for assisting in the stratification of risk in single patients. Besides, although glibenclamide is an antagonist of  $K_{ATP}$  channels, there are many potential nonspecific targets, including the inhibition of  $Na^+$  channels and the opening of  $Ca^{2+}$  channels (15). These alternative effects could confound the interpretation of the present study. However, it seems unlikely, because nicorandil significantly improved the effect of glibenclamide on LV mass.

In conclusion, our results show that  $K_{ATP}$  channels may play a pathogenetic role in diabetes mellitus-related ventricular hypertrophy. Given that LV mass reduction is accepted as a treatment goal, attenuation of LV mass in gliclazide-treated patients may have a potential beneficial effect, although we did not address the effect of attenuated LV mass on patient outcome. Our findings that different effects of short-term sulfonylurea drugs on LV mass should pave the way for additional large-scale clinical trial aimed at evaluating long-term clinical benefits of gliclazide therapy in type 2 diabetes mellitus.

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