

# Reduction of Central Blood Pressure in Response to Oral Glucose Loading Is Blunted in Patients With Diabetes Mellitus

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## BACKGROUND

Recent studies have shown that arterial stiffness is reduced after meal intake. We evaluated the acute response of central hemodynamics to glucose loading and the variation in their responses among normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes mellitus (DM).

## METHODS

The study enrolled 85 patients with known or suspected coronary artery disease who underwent a 75-g oral glucose tolerance test. Central hemodynamic measurements were assessed using radial applanation tonometry at fasting, 60, and 120 minutes after glucose loading.

## RESULTS

Glucose loading decreased the augmentation index normalized to a heart rate of 75 bpm (Alx@75) ( $81.6 \pm 13.9$  to  $74.5 \pm 14.1\%$ ,  $P < 0.01$ ) and central systolic blood pressure (SBP) ( $115 \pm 22$  to  $109 \pm 21$  mm Hg,  $P < 0.01$ ) at 120 minutes without a significant change in brachial SBP

( $126 \pm 25$  to  $125 \pm 25$  mm Hg,  $P = 0.93$ ). Glucose loading decreased central SBP in NGT and IGT groups but did not affect the DM group. Change in Alx@75 at 120 minutes after glucose loading was blunted in IGT and DM groups compared with the NGT group ( $-5.7 \pm 4.4$  vs.  $-3.6 \pm 4.1$  vs.  $-9.3 \pm 6.2\%$ ,  $P < 0.01$ ). Multivariate logistic regression analysis identified DM as an independent factor associated with the presence of blunted response of Alx to glucose loading.

## CONCLUSIONS

Oral glucose loading decreased central SBP and Alx@75 without a significant change in brachial SBP, and these central hemodynamic responses were blunted in patients with DM.

**Keywords:** applanation tonometry; arterial stiffness; augmentation index; hypertension; impaired glucose tolerance; insulin; normal glucose tolerance.

doi:10.1093/ajh/hpv120

Arterial stiffening causes an early return of pressure waves from reflectance sites.<sup>1,2</sup> The early return of the pressure waves increases central systolic blood pressure (SBP) and decreases central diastolic blood pressure.<sup>2,3</sup> Although various indices of arterial stiffness are described, there has been considerable interest in augmentation index (AIx), which is derived noninvasively by applanation tonometry of the radial artery.<sup>4-9</sup>

Recent studies demonstrated that arterial stiffness is reduced after meal intake in healthy adults,<sup>10-12</sup> and postprandial hemodynamic regulation is blunted in patients with metabolic syndrome.<sup>13</sup> While it is well known that impaired glucose tolerance (IGT) and diabetes mellitus (DM) are independent risk factors for cardiovascular disease,<sup>14-16</sup> and that DM leads to early arterial aging with increased arterial stiffness,<sup>17</sup> it remains unknown whether the presence of IGT or DM affect the acute response of AIx to hyperglycemia. The diagnosis of IGT and DM is usually made by an oral glucose tolerance test (OGTT), and it is of great interest whether the acute response of central and

peripheral hemodynamic measurements after a glucose load differs in normal glucose tolerance (NGT), IGT, and DM. Therefore, to address this issue, we first assessed the effects of oral glucose loading on central and peripheral hemodynamic measurements. Second, we evaluated the variation in their responses in NGT, IGT, and DM.

## METHODS

### Study population

Between August 2013 and July 2014, 387 patients were admitted to Hiroshima University Hospital for evaluating coronary artery disease. Patients with previous diagnosis of DM were excluded. Patients with previous cardiac or aortic surgery, atrial fibrillation, hemodialysis, left ventricular ejection fraction  $< 40\%$ , hemodynamically significant valvular heart disease, or systemic inflammatory conditions were also excluded because they could affect the central hemodynamic measurements. Consequently, 91 consecutive patients

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Initially submitted April 27, 2015; date of first revision May 27, 2015; accepted for publication June 30, 2015.

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underwent central hemodynamic measurements during OGTT. In 6 patients, the central hemodynamic measurements were failed and were excluded. Hence, 85 patients were enrolled in the study. Hypertension was defined as SBP  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or use of antihypertensive drugs. Dyslipidemia was defined as low density lipoprotein cholesterol  $\geq 140$  mg/dl, high density lipoprotein cholesterol  $< 40$  mg/dl, triglyceride  $\geq 150$  mg/dl, or use of lipid-lowering drugs.

### Oral glucose tolerance test

A standard OGTT with 75-g glucose was at 06:30 performed after overnight fasting. DM was defined as fasting glucose  $> 126$  mg/dl and/or glucose  $> 200$  mg/dl after 120 minutes, IGT was defined as fasting glucose  $< 126$  mg/dl and glucose of 140–200 mg/dl after 120 minutes, NGT was defined as fasting glucose  $< 126$  mg/dl and glucose  $< 140$  mg/dl after 120 minutes.<sup>18</sup>

### Central hemodynamic measurements

After 10 minutes of rest in a supine position, the left radial arterial waveform was recorded using an arterial applanation tonometry probe (Omron HEM-9000AI; Omron Healthcare, Kyoto, Japan) in a supine position. The brachial blood pressure was determined simultaneously in the right upper arm using the oscillometric method (Omron HEM-9000AI; Omron Healthcare). The first and second peak of radial artery waveform were automatically identified using the fourth derivative wave as the second and third zero crossing points, respectively (Figure 1).<sup>4</sup> SBP at the second peak (rSBP2) was obtained as an estimated central SBP. Previous

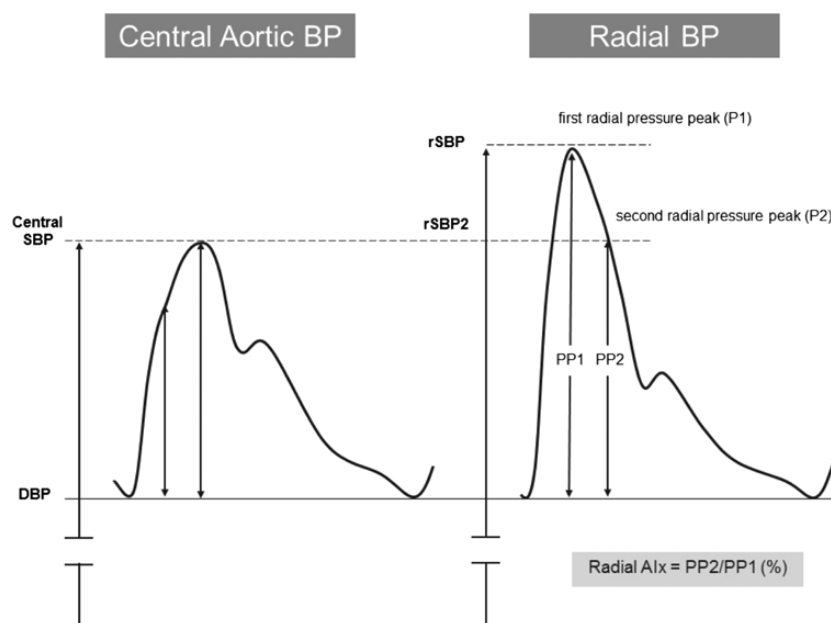
studies demonstrated that rSBP2 accorded well with central SBP measured by the invasive method.<sup>4–7</sup> Pulse pressure at the first peak (PP1) and second peak (PP2) were obtained, and AIx was calculated as the ratio of PP2 to PP1. AIx was corrected in accordance with the heart rate (AIx@75). The rSBP2 and AIx were determined for each pulse, and the mean values of all pulses measured for at least 30 seconds were used in the subsequent analysis. Central hemodynamic measurements were made at fasting (0 minute) and at 60 and 120 minutes after oral glucose loading. In first 20 consecutive patients whose central hemodynamic measurements were successfully obtained, the measurements were repeated the next day in a similar manner but with drinking only water without glucose in the same amount (225 ml) as in the glucose loading test.

### Blood sampling and laboratory examinations

Fasting samples were taken for plasma glucose, serum insulin, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride. Blood samples were drawn from the antecubital vein before glucose loading. Samples for plasma glucose and serum insulin were taken at 60 and 120 minutes after glucose loading, and shortly after the central hemodynamic measurements.

### Statistical analysis

Continuous variables were presented as mean  $\pm$  SD, and categorical variables were presented as frequencies and percentages. Multigroup comparisons of continuous variables were analyzed by 1-way analysis of variance followed by Bonferroni correction. Comparisons of time course



**Figure 1.** Schematic image of the central aortic (left) and radial aortic (right) pressure wave form. P1 and P2 indicate the first and second peak of the radial systolic blood pressure (SBP), respectively. SBP at the second peak (rSBP2) was obtained as an estimated central SBP. Radial augmentation index (AIx) was calculated as the ratio of pulse pressure at the second peak (PP2) to that of the first peak (PP1). Abbreviation: DBP, diastolic blood pressure.

curves of parameters before and after glucose loading or water intake were analyzed by 2-way analysis of variance for repeated measures by the Bonferroni correction for multi-paired comparisons. Univariate and stepwise multivariate logistic regression analyses were performed using clinical and hemodynamic parameters to determine the predictors of blunted response of AIx to oral glucose loading. Differences were considered significant if the  $P$  value was  $<0.05$ . Statistical analysis was conducted using JMP 10 software (SAS Institute, Tokyo, Japan).

## RESULTS

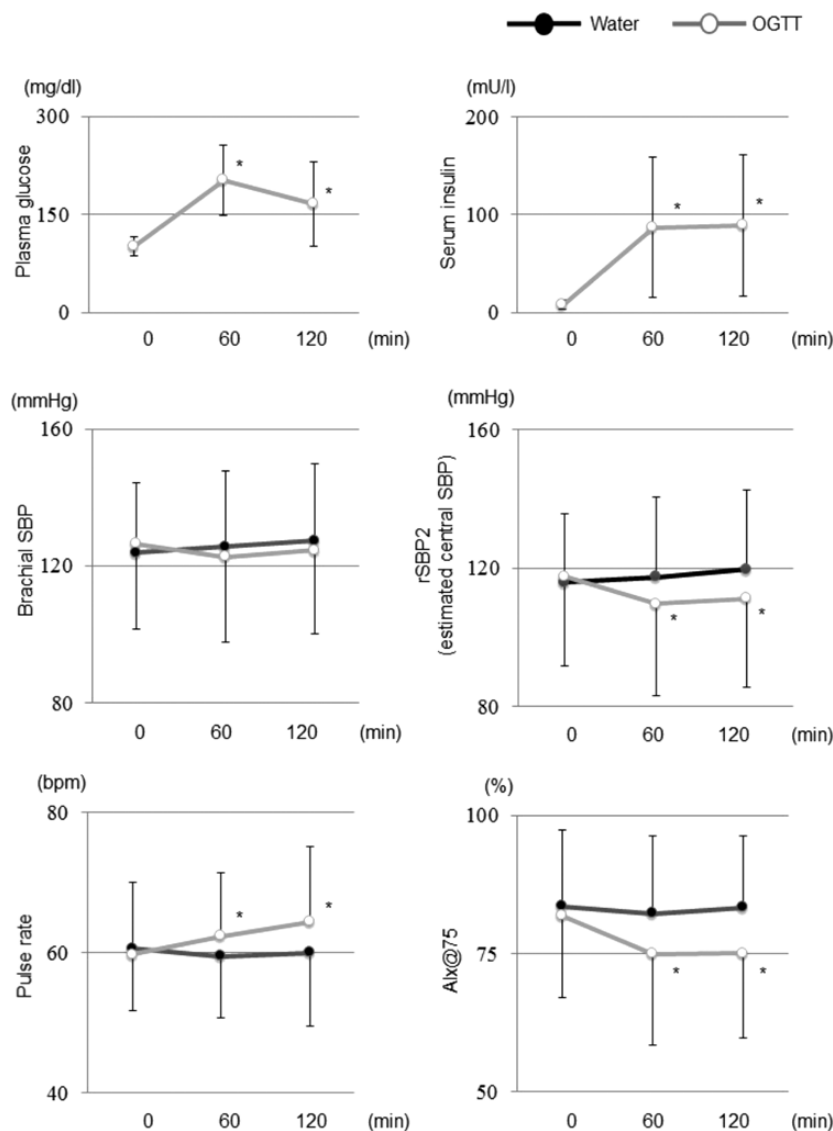
### Central hemodynamic responses to oral glucose loading

In the first 20 consecutive patients, central hemodynamic measurements were made after both the oral glucose

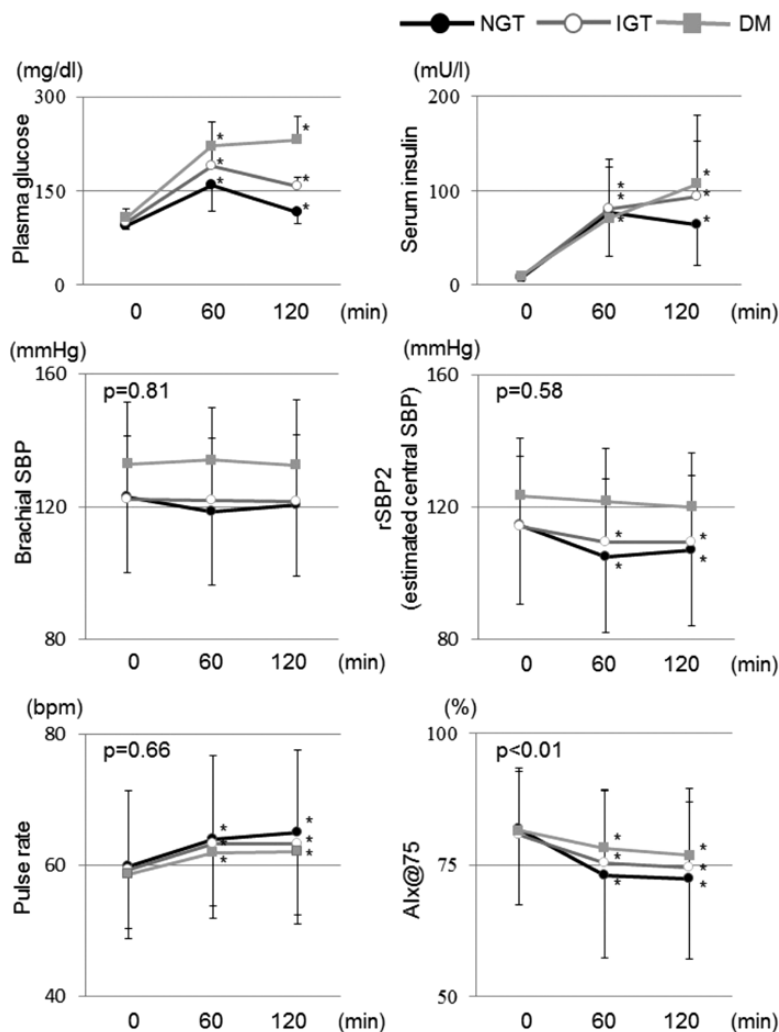
loading and water intake had been completed on the 2 different days (Figure 2). OGTT identified NGT in 6 patients, IGT in 10 patients, and DM in 4 patients. Oral glucose loading increased the plasma glucose ( $101 \pm 15$  to  $166 \pm 64$  mg/dl,  $P < 0.01$ ) and serum insulin ( $7.9 \pm 5.2$  to  $88.8 \pm 72.1$  mU/l,  $P < 0.01$ ) after 120 minutes but did not affect brachial SBP. Oral glucose loading decreased rSBP2 ( $118 \pm 26$  to  $111 \pm 267$  mm Hg,  $P < 0.01$ ) and AIx@75 ( $81.8 \pm 14.8$  to  $75.0 \pm 15.4\%$ ,  $P < 0.01$ ) after 120 minutes. Water intake, however, did not affect any central or peripheral hemodynamic measurements.

### Abnormal glucose tolerance and central hemodynamic responses to oral glucose loading

In 85 patients, central hemodynamic measurements were made after oral glucose loading (Figure 3). OGTT



**Figure 2.** The effects of water intake (solid circle,  $n = 20$ ) or oral glucose loading (open circle,  $n = 20$ ) on plasma glucose, serum insulin, and hemodynamic measurements. Data are expressed as mean  $\pm$  SD. \* $P < 0.01$  vs. baseline. Abbreviation: AIx, augmentation index; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.



**Figure 3.** Responses of plasma glucose, serum insulin, and hemodynamic measurements to glucose loading in patients with NGT (solid circle), IGT (open circle), and DM (solid square). Data are expressed as mean  $\pm$  SD. \* $P < 0.01$  vs. baseline.  $P$  values in the graph indicate variation between subgroup. Abbreviations: AIx, augmentation index; DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; SBP, systolic blood pressure.

identified NGT in 40 patients, IGT in 30 patients, and DM in 15 patients. Clinical characteristics of the 3 groups are shown in Table 1. There were no significant differences in baseline clinical and hemodynamic parameters among the 3 groups except for male sex, dyslipidemia, plasma glucose, and hemoglobin A1C.

In all groups, oral glucose loading increased plasma glucose and serum insulin after 120 minutes but had no significant effect on brachial SBP. Oral glucose loading decreased rSBP2 after 120 minutes in the NGT ( $115 \pm 24$  to  $107 \pm 23$  mm Hg,  $P < 0.01$ ) and the IGT groups ( $114 \pm 21$  to  $109 \pm 20$  mm Hg,  $P < 0.01$ ) but did not affect rSBP2 in the DM group ( $124 \pm 17$  to  $120 \pm 16$  mm Hg,  $P = 0.12$ ). Oral glucose loading also decreased AIx@75 after 120 minutes in the NGT ( $82.3 \pm 14.1$  to  $72.8 \pm 15.1\%$ ,  $P < 0.01$ ), IGT ( $80.8 \pm 12.6$  to  $74.5 \pm 12.4\%$ ,  $P < 0.01$ ), and DM groups ( $81.5 \pm 11.2$  to  $76.8 \pm 12.7\%$ ,  $P < 0.01$ ). Changes in AIx@75 at 60 and 120 minutes are shown in Figure 4. Compared with the NGT group, the change in AIx@75 was

significantly blunted at all times in both the DM and even the IGT groups.

#### Factors associated with blunted response of AIx

Blunted response of AIx was defined as a lower change in AIx@75 tertile at 120 minutes ( $<6.0\%$ ). Multiple logistic regression analysis was performed to identify independent variables associated with the blunted response of AIx. Age ( $\leq 70$  or  $>70$  years), sex, glucose tolerance (NGT, IGT, DM), serum insulin at 60 minutes ( $\leq 60$ ,  $60-100$ ,  $>100$  mU/l), and insulin resistance (yes/no) were entered into a stepwise analysis. After the stepwise analysis, age ( $>70$  years), sex, DM, and serum insulin at 60 minutes ( $60-100$  mU/l,  $>100$  mU/l) were selected as variables. These variables in addition to IGT were then entered into the multiple logistic regression analysis. Multivariate logistic regression analysis identified DM (odds ratio: 4.17, 95% confidence interval: 1.11–17.76,  $P = 0.034$ ) and serum insulin at 60 minutes ( $>60$  mU/l) as

**Table 1.** Characteristics of the patients with NGT, IGT, and DM

	Patients with NGT (n = 40)	Patients with IGT (n = 30)	Patients with DM (n = 15)	P value
Clinical characteristics				
Age (years)	67.0 ± 12.9	67.7 ± 9.6	69.2 ± 11.5	0.82
Male gender, n (%)	29 (73%)	24 (80%)	15 (100%)*†	0.02
Height (cm)	163.3 ± 8.7	163.7 ± 7.0	164.5 ± 6.7	0.89
Weight (kg)	61.8 ± 9.8	63.7 ± 11.3	69.1 ± 11.4	0.08
Body mass index (kg/m <sup>2</sup> )	23.1 ± 2.9	23.7 ± 3.8	25.4 ± 3.2	0.07
Hypertension, n (%)	25 (63%)	22 (73%)	13 (87%)	0.18
Dyslipidemia, n (%)	24 (60%)	24 (80%)*	15 (100%)*†	<0.01
Cigarette smoking, n (%)	23 (58%)	20 (67%)	13 (87%)	0.10
Fasting plasma glucose (mg/dl)	95 ± 7	99 ± 11	107 ± 15*	<0.01
Fasting serum insulin (mU/l)	7.9 ± 3.6	9.3 ± 5.4	9.5 ± 5.3	0.37
Hemoglobin A1C (%)	5.6 ± 0.3	5.9 ± 0.3*	6.1 ± 0.4*†	<0.01
HOMA-R	1.9 ± 0.9	2.3 ± 1.4	2.6 ± 1.6	0.13
LDL cholesterol (mg/dl)	103 ± 30	95 ± 26	97 ± 32	0.45
HDL cholesterol (mg/dl)	55 ± 16	49 ± 13	47 ± 9	0.14
Triglyceride (mg/dl)	122 ± 63	137 ± 76	135 ± 69	0.62
Serum creatinine (mg/dl)	0.9 ± 0.3	1.0 ± 0.3	1.0 ± 0.2	0.18
Brachial SBP (mm Hg)	123 ± 23	122 ± 19	133 ± 19	0.24
Brachial DBP (mm Hg)	64 ± 11	65 ± 10	70 ± 13	0.20
Pulse rate (beats/minutes)	60 ± 12	60 ± 9	59 ± 10	0.94
Augmentation index (%)	88.2 ± 15.9	87.4 ± 12.9	88.4 ± 12.8	0.97
Augmentation index@75 (%)	81.7 ± 14.3	80.8 ± 12.6	81.5 ± 11.2	0.96
rSBP2 (estimated central SBP) (mm Hg)	115 ± 24	114 ± 21	124 ± 17	0.35

Values are mean ± SD or number of participants (%).

Abbreviations: DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high density lipoprotein; HOMA-R, homeostasis model assessment ratio; IGT, impaired glucose tolerance; LDL, low density lipoprotein; NGT, normal glucose tolerance; SBP, systolic blood pressure.

\*P < 0.05 vs. NGT.

†P < 0.05 vs. IGT.

independent factors associated with blunted response of AIx (Table 2).

## DISCUSSION

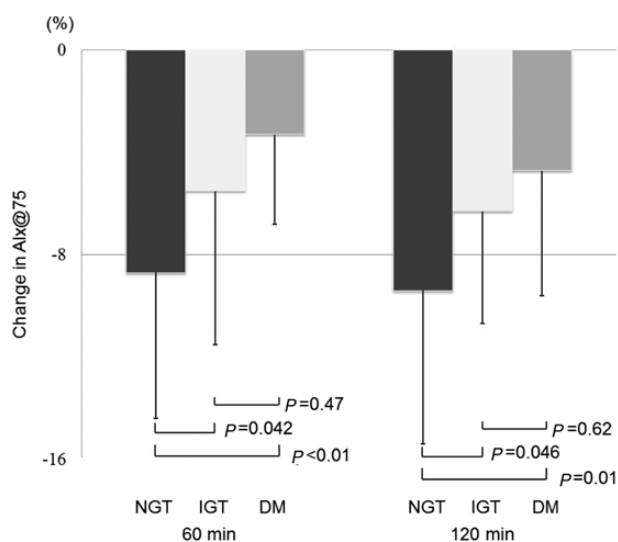
We demonstrated the following: (i) oral glucose loading significantly decreased rSBP2 and AIx without a significant change in brachial SBP, (ii) the response of AIx to oral glucose loading was impaired in patients with IGT or DM, and (iii) a significant reduction of rSBP2 to oral glucose loading was absent in patients with DM, and DM was an independent factor of blunted response of AIx to glucose loading.

### Effects of glucose loading on hemodynamic regulation

Arterial stiffness is a major determinant of central blood pressure. An increase in tone of small arteries causes an increase in central SBP and a decrease in central diastolic blood pressure, and they are associated with increased afterload of the left ventricle and decreased coronary blood flow,

respectively.<sup>2,3</sup> A number of studies have examined the acute effects of a meal on arterial stiffness. Ahuja *et al.*<sup>10</sup> reported that a mixed meal (311 kcal, 63% carbohydrate, 27% fat, 10% protein) decreased central SBP and AIx in healthy subjects. Mixed meal study by Taylor *et al.*<sup>12</sup> (661 kcal, 58% carbohydrate, 28% fat, 14% protein) and Funada *et al.*<sup>13</sup> (500 kcal, carbohydrate 51 g, fat 28 g, protein 10 g) also demonstrated similar effects on central hemodynamic measurements in healthy subjects and in patients with metabolic syndrome, respectively. In our study, we demonstrated that pure glucose (300 kcal) decreased rSBP2 and AIx. Acute hyperglycemia has been shown to have sympathoexcitatory effects.<sup>19</sup> Previous studies using hyperglycemic clamp technique have shown that acute hyperglycemia rapidly increases AIx in healthy subjects or in patients with type 1 diabetes.<sup>20</sup> Because acute hyperglycemia itself has been shown to be a promoting factor of AIx, we hypothesized that oral glucose loading might increase AIx through the sympathoexcitatory effect. However, our study demonstrated that oral glucose loading decreased rSBP2 and AIx without significant change

in brachial SBP. Although the precise mechanism for the decreasing of rSBP2 and AIx remains unclear, acute hyperinsulinemia reacting to the oral glucose loading is probably related to our findings. In support of the hypothesis, Westerbacka *et al.*<sup>21</sup> showed that insulin rapidly decreased AIx in healthy subjects by using the euglycemic insulin clamp technique. Tamminen *et al.*<sup>22</sup> also found similar effects of insulin in patients with type 2 DM. In resistance arteries, insulin exerts vasodilator action that is significantly abolished by co-infusion of L-N-mono-methyl-arginine, which competitively antagonizes the synthesis of nitric oxide.<sup>23</sup> This implies that insulin induces vasodilation by activation of the endothelial L-arginine nitric oxide pathway.



**Figure 4.** Changes in AIx@75 at 60 and 120 minutes after glucose loading in patients with NGT (black bar), IGT (light gray bar), and DM (dark gray bar). Data are expressed as mean  $\pm$  SD. Abbreviations: AIx, augmentation index; DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

In our study, we found an approximately 11-fold increase in the concentration of insulin after oral glucose loading. Based on ours and previous studies, central hemodynamic measurements were influenced by both acute hyperglycemia and hyperinsulinemia, and they were probably regulated mainly by hyperinsulinemia rather than hyperglycemia. Our results suggest that insulin-induced endothelial-dependent vasodilation led to a distal shift of the pressure wave reflection side, thereby reducing AIx and central SBP without significant change in the brachial SBP.

#### Effects of glucose tolerance on central hemodynamic responses to oral glucose loading

We found no significant difference in basal central hemodynamic measurements among NGT, IGT, and DM groups. However, changes in rSBP2 and AIx after oral glucose loading were progressively blunted with the NGT group least blunted, the IGT group more blunted, and the DM group most blunted. These findings may be supported by a previous study using the euglycemic insulin clamp technique that showed a more blunted response of AIx to insulin in patients with type 2 DM compared with those without.<sup>22</sup>

IGT and type 2 DM are considered as a heterogeneous metabolic disorder involving variable combinations of impaired insulin secretion and insulin resistance. The mechanisms responsible for postprandial hyperglycemia in patients with type 2 DM and in individuals with IGT are basically the same, but abnormalities are more severe in patients with type 2 DM.<sup>24,25</sup> Recent studies have shown that flow-mediated vasodilation is more impaired in IGT than in NGT groups, and the impairment is more remarkable in DM than IGT group.<sup>26,27</sup> This suggests that endothelial function is progressively impaired with the NGT group least impaired, the IGT group more impaired, and the DM group most impaired. Based on previous studies and on our results, we suggest that blunted central hemodynamic responses to oral glucose loading in the DM group were due in part to the

**Table 2.** Multiple logistic regression analysis of the relationships between the blunted response of AIx@75 and variables

Covariates		Odds ratio	95% CI	P value
Age	<70 years	1.00		
	>70 years	0.39	0.14–1.01	0.054
Sex	Men	1.00		
	Women	2.21	0.66–7.83	0.198
Glucose tolerance	NGT	1.00		
	IGT	1.15	0.40–3.31	0.791
	DM	4.17	1.11–17.76	0.034
Insulin secretion at 60 minutes	<60 mU/l	1.00		
	60–100 mU/l	0.24	0.08–0.71	0.010
	>100 mU/l	0.28	0.08–0.96	0.042

Blunted response of AIx was defined as change in AIx@75 tertile at 120 minutes (<6.0%).

Abbreviations: AIx, augmentation index; CI, confidence interval; DM, diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

$R^2 = 0.12$ ,  $P = 0.027$ .

impaired insulin-induced endothelial-dependent vasodilation at least in part.

### Clinical implication

Recent studies have shown that noninvasively determined central blood pressure is more closely related to cardiovascular outcomes than brachial blood pressure.<sup>28–30</sup> In our study, there was no significant difference in basal central SBP among the 3 groups. Whether the differences in central hemodynamic responses to glucose load among NGT, IGT, and DM are clinically important, remains an important question. We do believe, however, that the blunted response of the central hemodynamic measurements to a glucose load may have a higher risk for future cardiovascular events because of the persistently high levels of central SBP.

### Limitations

Our study has several potential limitations. First, this study focused on patients with known or suspected coronary artery disease. Therefore, most patients had coronary risk factors and received antihypertensive medication. The medication was continued during the study owing to ethical considerations until the night before testing for the study. Although the use of renin-angiotensin system inhibitor,  $\beta$ -blocker, and diuretics were similar among the 3 groups, the use of calcium channel blocker was higher in the DM group. Therefore, there is a possibility that ongoing atherosclerosis process or antihypertensive medications may have had some effects on the central hemodynamic responses. Second, central hemodynamic measurements were obtained only with the HEM-9000 AI. It is known that underestimation of central SBP using the rSBP2 method may occur when the systolic pressure is highest before the inflection.<sup>31</sup> However, previous studies<sup>4,7,8,31–34</sup> have shown that the rSBP2 method approximates central SBP using the invasive method or the generalized transfer function, and thereby the rSBP2 method is reliable for evaluating the central SBP response. Third, central hemodynamic measurements were obtained only 3 times after oral glucose loading, allowing a possibility that their peak changes were underestimated. In addition, their time courses beyond 120 minutes remain unclear. Further studies with more frequent and precise times courses would provide clarification. Finally, the small study sample size and the differences of baseline characteristics such as sex, and the prevalence of dyslipidemia among the 3 groups are major limitations in this study.

### CONCLUSION

In conclusion, oral glucose loading decreased central SBP and AIx without a significant change in brachial SBP, and these central hemodynamic responses were blunted in patients with DM.

### DISCLOSURE

The authors declared no conflict of interest.

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