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ORIGINAL ARTICLE

The impact of intraday glucose variability on coronary artery spasm in patients with dysglycemia

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Abstract
Impaired glucose metabolism is associated with an increased risk of cardiovascular complications, and coronary artery spasm is thought to underlie the development of coronary artery disease. Intraday glucose variability (GV) accelerates oxidative stress and inflammatory cytokine release, but its impact on coronary artery spasm remains unclear. This study investigated the relationship between intraday GV and coronary artery spasm. The study included 50 patients with dysglycemia and suspected coronary spastic angina. GV was analyzed by 24-h monitoring of the blood glucose concentration using a flash glucose monitoring system. The mean amplitude of glycemic excursion (MAGE) was calculated as an index of GV. Coronary artery spasm was assessed using the intracoronary acetylcholine provocation test. Coronary spasm was defined as acetylcholine-induced total or subtotal coronary occlusion. Changes in vessel diameter in response to acetylcholine were evaluated with quantitative coronary angiography. Coronary artery spasms were observed in 21 patients (42%). MAGE was significantly higher in patients with spasms compared to those without spasms (127.5 ± 33.5 vs. 91.4 ± 37.6, $p < 0.01$). Regression analysis showed a positive correlation between MAGE levels and coronary diameter changes induced by acetylcholine ($r = 0.47$, $p < 0.01$). In multiple regression analysis, MAGE was independently associated with acetylcholine-induced coronary diameter change ($\beta = 0.47$, $p < 0.01$). Intraday GV was associated with coronary artery spasm in patients with dysglycemia.

Keywords Dysglycemia · Glucose variability · Flash glucose monitoring · Coronary spasm

Introduction

Impaired glucose metabolism, as seen in diabetes mellitus, is associated with an increased risk of cardiovascular complications [1], and cardiovascular disease is the major cause of death in patients with diabetes [2]. Notably, microvascular complications can be ameliorated via glycemic control, i.e., by controlling fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels [3]. However, intensive glycemic control has no marked effect on macrovascular complications; indeed, mortality can increase due to severe hypoglycemia [4]. Intraday glycemic variability (GV), which accelerates oxidative stress [5] and inflammatory cytokine release [6], is suggested to be one of the determinants of the presence and severity of coronary artery disease [7]. Furthermore, in patients with acute coronary syndrome, intraday GV is associated with coronary plaque vulnerability [8] and predicts subsequent cardiac events [9].

Coronary artery spasm has been shown to play an important role in the pathogenesis of variant angina pectoris and various types of ischemic heart disease, including sudden cardiac death, syncope and acute coronary syndrome [10–13]. Therefore, it is important to clarify the underlying cause of coronary artery spasm in order to prevent and treat coronary artery disease. The impact of intraday GV on coronary artery spasm is currently unclear. The aim of this study was to investigate the relationship between intraday GV as determined by a flash continuous glucose monitoring (FGM) system and coronary artery spasm as evaluated by intracoronary acetylcholine administration.

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Materials and methods

Study population

A cross-sectional observational study was conducted in patients with dysglycemia who were clinically suspected of coronary spastic angina who underwent coronary angiography with the acetylcholine spasm provocation test. From January 2017 to August 2018, 24-h blood glucose monitoring using FGM was successfully conducted in consecutive 50 patients. In this study, dysglycemia was defined as type 2 diabetes or impaired fasting glucose (FPG ≥ 110 mg/dL). Type 2 diabetes was defined according to the diagnostic criteria of the American Diabetes Association or by the patient's use of insulin or glucose-lowering drugs. Hypertension was defined as systolic blood pressure (BP) greater than 140 mmHg and/or diastolic BP greater than 90 mmHg or current treatment with antihypertensive medication. The study protocol was approved by our institution's human research committee. Informed consent was obtained from all individual participants included in the study.

Flash continuous blood glucose monitoring

All subjects were equipped with sensor-based FGM systems (Freestyle Libre Pro; Abbott Diabetes Care, Alameda, CA, USA) on the back of the upper arm and were monitored for at least 24 consecutive hours. Monitoring was started at 1 h after the acetylcholine provocation test. The sensor is calibrated in the factory and does not require calibration. The interstitial glucose concentration is automatically captured and stored on the subcutaneous sensor every 15 min. During glucose monitoring, all patients received optimal meals (25 kcal/kg of their ideal body weight; 60% carbohydrate, 15–20% protein, and 20–25% fat). The maximum, minimum, and mean blood glucose levels, the standard deviation (SD), and the mean amplitude of glycemic excursions (MAGE) were determined. MAGE represents blood GV and is calculated by measuring the arithmetic mean of the difference between consecutive peaks to nadirs, providing that the differences are greater than the SD of the mean blood glucose value [14].

Blood sampling

Venous blood samples were collected after overnight fasting. HbA1c, fasting glucose, high-sensitivity C-reactive protein, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined. Low density cholesterol was measured with a direct homogeneous assay (Kyowa Medex Co., Tokyo, Japan).

Acetylcholine provocation test

All anti-anginal drugs except for sublingual nitroglycerin and metformin were withdrawn at least 48 h before cardiac catheterization. Coronary angiography was performed with the standard Judkins technique. When the diagnostic angiography did not show significant stenosis (> 75% diameter stenosis by visual estimate), intracoronary acetylcholine was administered according to the guidelines of the Japanese Circulation Society [15]: 20 or 50 μg in the right coronary arteries and 20, 50, or 100 μg in the left coronary arteries. Before acetylcholine injection, a temporary pacing electrode was inserted into the right ventricle to perform backup pacing. Subsequently, intracoronary nitroglycerin was injected to relieve the coronary artery spasm. A coronary artery spasm was defined as total or subtotal occlusion (visually > 90% stenosis compared with the relaxed state after nitroglycerin) that was associated with an ischemic ECG change (transient ST elevation > 0.1 mV or ST depression < 0.1 mV in more than 2 contiguous leads) and concurrent chest pain similar to that of a spontaneous attack. The patients who did not fulfill the criteria of spasm were classified as normal coronary vasoreactivity defined as diameter change of visually < 25% or moderate coronary vasoeractivity as ≥ 25%.

Quantitative coronary angiography

Offline quantitative coronary angiography (QCA) was performed with an automated edge detection program (the Cardiovascular Measurement System, Medical Imaging Systems, Leiden, The Netherlands). After maximal intracoronary infusion of acetylcholine and nitroglycerin, the mean luminal diameter was measured at a segment beginning from 20 mm distal of the right coronary artery ostium to bifurcation of posterior descending artery in a 50° left anterior oblique view. The percent changes in coronary artery diameter were calculated as follows: % diameter change = (mean luminal diameter after nitroglycerin infusion − mean luminal diameter after acetylcholine infusion)/mean luminal diameter after nitroglycerin infusion × 100.

Statistical analysis

Quantitative variables are reported as means ± SDs. Discrete variables are reported as numbers and percentages. We used unpaired t tests and one-way ANOVA tests to compare quantitative variables and χ^2 tests and Fisher's exact tests for discrete variables.

Correlations between the glucose parameters and changes in coronary diameter in response to acetylcholine were estimated with Pearson's correlation coefficients. Multivariate regression analysis was performed to investigate the relationships between the diameter change in response to acetylcholine and other variables. Covariates used in the multivariate model were male sex, MAGE, and smoking. Significance was defined as $p < 0.05$. Data were analyzed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

The baseline patient characteristics are presented in Table 1. Acetylcholine induced coronary spasm in 21 patients (42%). Coronary spasms were provoked more frequently in males than in females. Smoking was more common in patients with coronary spasm. The patients were divided into the two groups according to the median MAGE of 103 (Table 2). Diabetes and total spasms were more frequently observed and percent coronary diameter change in response to acetylcholine was significantly larger in the high MAGE group. The patients' glucose parameters are listed in Table 3. Patients that experienced spasms had higher SDs and MAGE levels than those that did not experience spasms. In the non-spasm group, moderate vasoreactivity was observed in 13 patients and in the spasm group, total spasm in 8 patients. Higher MAGE was associated with increased vasoreactivity (Fig. 1). Of the glucose parameters, MAGE and SD showed significant correlation with changes in coronary diameter, but HbA1c and FPG did not (Fig. 2). Table 4 shows the results of multivariate linear regression analysis, which indicated that MAGE was significantly associated with changes in coronary luminal diameter.

Table 1 Baseline patient characteristics

Variable	All $N=50$	Spasm group $n=21$	Non-spasm group $n=29$	p
Age, years	70.3 ± 8.9	69.6 ± 9.0	70.9 ± 9.0	0.61
Male	30 (60%)	18 (86%)	12 (41%)	< 0.01
BMI, kg/m^2	23.7 ± 3.5	23.5 ± 2.9	23.8 ± 4.0	0.80
Diabetes	22 (44%)	10 (48%)	12 (41%)	0.66
Hypertension	38 (76%)	18 (86%)	20 (69%)	0.17
Dyslipidemia	37 (74%)	16 (76%)	21 (72%)	0.99
Smoking	32 (64%)	17 (81%)	15 (52%)	0.04
Total cholesterol, ng/dL	187.0 ± 38.6	187.0 ± 40.2	186.9 ± 38.1	0.99
LDL, mg/dL	105.6 ± 30.2	103.4 ± 31.1	107.2 ± 30.0	0.67
HDL, mg/dL	59.7 ± 18.2	62.1 ± 20.3	58.0 ± 16.7	0.44
TG, mg/dL	131.8 ± 86.3	139.9 ± 107.4	125.9 ± 68.5	0.58
CRP, mg/dL	0.12 ± 0.21	0.16 ± 0.30	0.09 ± 0.07	0.23
Cr, mg/dL	0.82 ± 0.20	0.85 ± 0.18	0.80 ± 0.21	0.40
Medications				
Ca-channel blocker	26 (52%)	10 (48%)	16 (55%)	0.60
ACE-inhibitor/ARB	24 (48%)	13 (62%)	11 (38%)	0.09
Beta blocker	13 (26%)	4 (19%)	9 (31%)	0.51
Nitrate	6 (12%)	4 (19%)	2 (7%)	0.22
Statin	31 (62%)	13 (62%)	18 (62%)	0.99
Oral anti-diabetic drugs	17 (34%)	6 (29%)	11(38%)	0.49
Metformin	8 (16%)	4 (19%)	4 (14%)	0.71
DPP4-I	15 (30%)	5 (24%)	10 (34%)	0.54
SU	3 (6%)	0	3 (10%)	0.25
Pioglitazone	2 (4%)	0	2 (7%)	0.50
α-GI	2 (4%)	1 (5%)	1 (3%)	0.99
SGLT2-I	3 (6%)	2 (10%)	1 (3%)	0.57
Insulin	3 (6%)	1 (5%)	2 (7%)	0.99

Data represent either n (%) or the mean ± SD

α-GI a-glucosidase inhibitor, *ACE-inhibitor/ARB* angiotensin converting enzyme-inhibitor/angiotensin receptor blocker, *BMI* body mass index, *Cr* creatinine, *CRP* C-reactive protein, *DPP4-I* dipeptidyl peptidase-4 inhibitor, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SGLT2-I* sodium-glucose Co-transporter 2 inhibitors, *SU* sulfonylurea, *TG* triglycerides

Table 2 Relationship between glycemic variability and clinical and lesion characteristics

Variable	High MAGE group $n=25$	Low MAGE group $n=25$	p
Age, years	69.7 ± 8.7	71.0 ± 9.3	0.63
Male	17 (68%)	13 (52%)	0.25
BMI, kg/m^2	24.7 ± 5.3	23.3 ± 3.1	0.26
Diabetes	15 (60%)	6 (24%)	< 0.01
Hypertension	21 (84%)	17 (68%)	0.19
Dyslipidemia	17 (68%)	20 (80%)	0.33
Smoking	18 (72%)	14 (56%)	0.24
Total cholesterol, ng/dL	187.6 ± 40.0	186.3 ± 38.0	0.91
LDL, mg/dL	105.0 ± 33.8	106.2 ± 26.7	0.89
HDL, mg/dL	62.4 ± 18.7	57.0 ± 17.6	0.30
TG, mg/dL	122.1 ± 65.4	141.5 ± 103.5	0.43
CRP, mg/dL	0.15 ± 0.28	0.09 ± 0.08	0.30
Cr, mg/dL	0.82 ± 0.20	0.82 ± 0.19	0.94
Hypoglycemia	10 (40%)	8 (32%)	0.56
Oral anti-diabetic drugs	12 (48%)	5 (20%)	0.07
Insulin	3 (12%)	0	0.23
Spasm type			< 0.01
No spasm	9 (18%)	20 (80%)	
Subtotal	9 (36%)	4 (16%)	
Total	7 (28%)	1 (4%)	
Quantitative coronary angiography			
Mean diameter after ACH, mm	2.09 ± 0.59	2.38 ± 0.60	0.10
Mean diameter after NTG, mm	2.99 ± 0.62	2.80 ± 0.51	0.22
% diameter change, %	30.3 ± 14.0	15.8 ± 11.5	< 0.01

Data represent either n (%) or the mean ± SD

ACH acetylcholine, *BMI* body mass index, *Cr* creatinine, *CRP* C-reactive protein, *HDL* high-density lipoprotein, *MAGE* mean amplitude of glycemic excursion, *LDL* low-density lipoprotein, *NTG* nitroglycerin, *TG* triglycerides

Table 3 Glucose parameters

Variable	All subjects $n=50$	Spasm group $n=21$	Non-spasm group $n=29$	p value
Fasting blood glucose, mg/dl	124.0 ± 29.5	122.2 ± 24.9	125.3 ± 32.9	0.72
HbA1c, %	6.33 ± 0.90	6.22 ± 0.78	6.41 ± 0.98	0.46
Flash glucose monitoring system				
Maximum blood glucose, mg/dl	219.7 ± 55.7	237.8 ± 47.6	206.7 ± 58.2	0.05
Minimal blood glucose, mg/dl	63.2 ± 19.2	62.4 ± 16.2	63.6 ± 21.4	0.81
Mean blood glucose, mg/dl	122.1 ± 32.5	126.0 ± 28.1	119.3 ± 35.5	0.48
SD	40.2 ± 15.3	46.7 ± 12.9	35.5 ± 15.3	< 0.01
MAGE	106.6 ± 39.9	127.5 ± 33.5	91.4 ± 37.6	< 0.01

Data are reported as means ± SDs

MAGE mean amplitude of glycemic excursion, *SD* standard deviation

Discussion

To our knowledge, this is the first observational study to report the clinical impact of intraday GV on coronary artery spasm as assessed by the acetylcholine infusion test. Our main finding was that GV, as quantified with the FGM system, was a significant predictor of acetylcholine-induced coronary spasms and that GV correlated with changes in vessel diameter in response to acetylcholine.

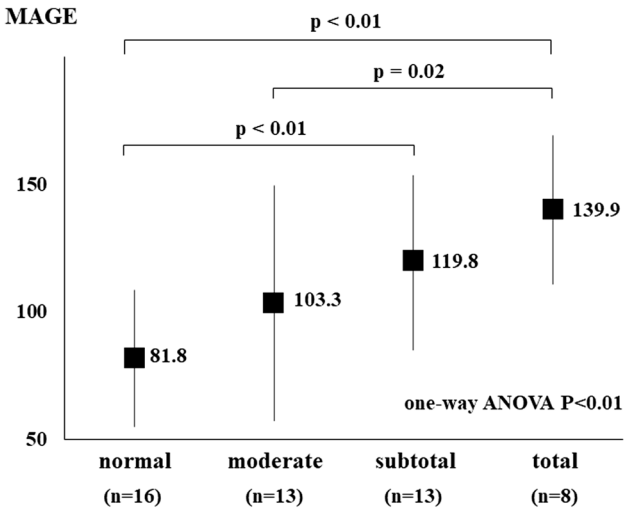

Fig. 1 Comparison of mean amplitude of glycemic excursions (MAGE) among patients with normal vasoreactivity, moderate vasoreactivity, subtotal spasm and total spasm

Intraday glycemic variability measured by the flash glucose monitoring system as an index of abnormal glucose regulation

The prevalence of abnormal glucose metabolism, which is a strong risk factor for coronary artery disease, is increasing worldwide, and HbA1c is a convenient glycemic status marker for assessing chronic sustained hyperglycemia. However, large clinical studies have shown that controlling HbA1c in patients with dysglycemia is not enough to reduce the rate of macrovascular complications, since hypoglycemia resulting from intensive glycemic control can lead to cardiovascular events [3, 4]. It has been suggested that postprandial hyperglycemic spikes that occur during the early stage of glucose intolerance may be a significant predictor of atherosclerosis [16, 17]. Impaired glucose metabolism disorders are not limited to chronic sustained hyperglycemia; rather, they can also include acute glucose swings. Because of the potential relationship of abnormal glucose excursion, such as hypoglycemia and post-challenge hyperglycemia, to

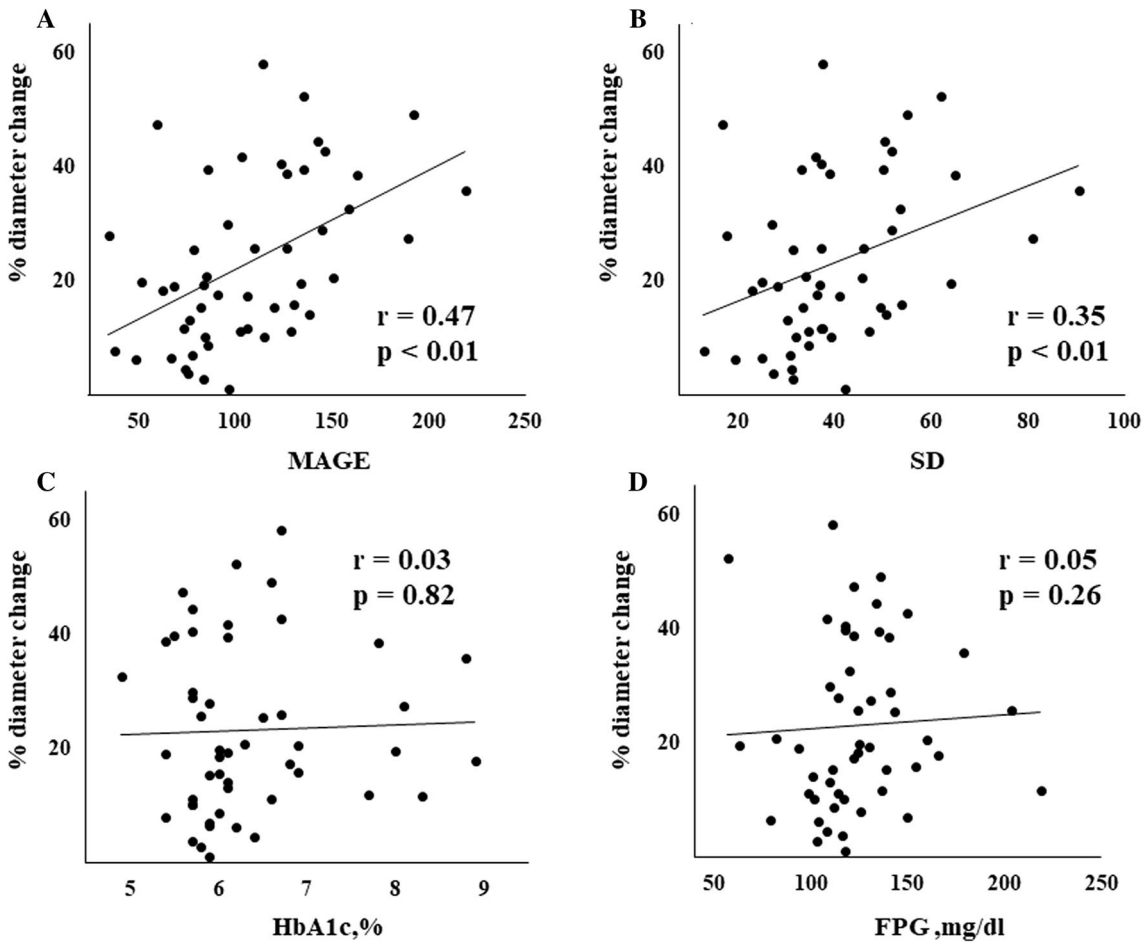

Fig. 2 The relationship between glucose parameters and changes in coronary luminal diameter in response to acetylcholine. Correlations are shown between the percent diameter change and **a** the mean amplitude of glycemic excursion (MAGE), **b** the standard deviation (SD), **c** hemoglobin A1c (HbA1c), and **d** fasting plasma glucose (FPG)

Table 4 Multivariate regression analysis of changes in coronary luminal diameter in response to acetylcholine

Variable	Standardized coefficient β	Standard error	*t*	*p* value
MAGE	0.47	0.05	3.50	< 0.01
Male sex	0.11	4.71	0.68	0.50
Smoking	− 0.06	4.85	− 0.36	0.72

MAGE mean amplitude of glycemic excursion

cardiovascular disease, recent studies have recognized that intraday blood GV is an important index associated with cardiovascular risk compared to conventional blood glucose indices. In order to evaluate the cardiovascular risk, both the mean level of glycemic control and the extent of GV needed to be assessed. FGM can measure interstitial glucose concentrations with an accuracy that is similar to that of a continuous blood glucose monitoring system [18] and is an effective tool for evaluating intraday GV.

The relationship between glucose variability and cardiovascular complications

Previous studies that used continuous glucose monitoring systems have shown that intraday GV is associated with cardiovascular complication severity. The presence and severity of CAD as detected by coronary angiography are associated with GV [7], and GV correlates with coronary plaque vulnerability in intravascular imaging modalities [8]. Fluctuations in blood glucose levels play a significant role in peripheral vascular endothelial dysfunction [19]. Finally, in patients with acute myocardial infarction, elevated MAGE is a strong predictor of cardiac mortality [9]. In our study, GV, as represented by MAGE, was associated with coronary artery spasm. Although the underlying pathogenesis of GV-related cardiovascular complications is not fully understood, several mechanisms have been suggested. GV activates oxidative stress [5], which is increased in patients with coronary endothelial dysfunction, as we reported previously [20]. Furthermore, GV accelerates inflammatory cytokine release [6], increases reactive oxygen species [21], and reduces NO production [22]. Sympathetic activation caused by acute hyperglycemia could induce coronary microvascular dysfunction [23]. Notably, intermittent hyperglycemia increases endothelial cell apoptosis more than chronic hyperglycemia [24]. GV can induce the expression of adhesion molecules and result in the excessive formation of advanced glycation end products via activation of nuclear factor κB and the protein kinase C pathway [25, 26]. Platelet activation is enhanced and thrombotic properties may be increased in acute hyperglycemia [27].

Clinical implications

Coronary artery spasm is associated with cardiovascular adverse events including variant angina, acute coronary syndrome and sudden cardiac death. Interventions that ameliorate coronary artery spasm are important for patients that have a high risk for coronary artery disease, such as those with diabetes. Although coronary spasm can be usually suppressed with vasodilators such as calcium channel blockers and nitrates, some patients intractable to these drugs are present [28]. In patients with drug-resistant coronary spasm, some interventions with different mechanisms are needed. Our results showed that GV was an important marker of acetylcholine induced coronary artery spasm. Although a prospective study is required to investigate whether controlling GV could improve coronary artery spasm and future clinical outcomes, our findings suggest that controlling GV by lifestyle modification and/or by pharmacological treatment may add an incremental effect for patients in whom control of coronary spasm is difficult.

Limitations

This study has some limitations. First, this was an observational study that included a relatively small number of Japanese patients who were recruited at a single center. Our findings should be confirmed in a larger population. Second, we did not measure markers of oxidative stress, inflammation, or sympathetic activity. Third, FGM was performed during hospitalization, but diet may be quite different outside of a hospital setting. Fourth, FGM was started at 1 h after provocation test, which itself might affect the FGM results. Fifth, we analyzed coronary luminal diameter by QCA only in the RCA. Therefore, the impact of GV on multivessel spasm remains unknown. Finally, we did not determine whether there was a causal relationship between GV and coronary artery spasm due to the cross-sectional study design.

Conclusion

Intraday GV was associated with coronary artery spasm in patients with dysglycemia.

Compliance with ethical standards

Conflict of interest This work was supported by a Grant-in-Aid for Research from Nagoya City University.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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