Significance of day-to-day glucose variability in heart failure patients after acute coronary syndrome

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Abstract

Background: Several studies have recently addressed the importance of glycemic variability (GV) in patients with acute coronary syndrome (ACS). Although daily GV measures, such as mean amplitude of glycemic excursions, are established predictors of poor prognosis in patients with ACS, the clinical significance of day-to-day GV remains to be fully elucidated. We therefore monitored day-to-day GV in patients with ACS to examine its significance.

Methods: In 25 patients with ACS, glucose levels were monitored for 14 days using a flash continuous glucose monitoring system. Mean of daily differences (MODD) was calculated as a marker of day-to-day GV. N-terminal pro–brain natriuretic peptide (NT-proBNP) was evaluated within 4 days after hospitalization. Cardiac function (left ventricular end-diastolic volume, left ventricular ejection fraction, stroke volume) was assessed by echocardiography in the acute and chronic phases.

Results: Of the 25 patients, 8 (32%) were diagnosed with diabetes, and continuous glucose monitoring (CGM)-based MODD was high (10.3 to 42.3) in 24 patients (96%). Although MODD did not correlate with max CK, there was a positive correlation between J-index, high blood glucose index, and NT-proBNP ($r = 0.83$, $p < 0.001$; $r = 0.85$, $p < 0.001$; $r = 0.41$, $p = 0.042$, respectively).

Conclusion: In patients with ACS, MODD was associated with NT-proBNP. These results suggest that monitoring day-to-day GV in ACS patients may be useful for evaluating worsening cardiac function independent of myocardial infarction after ACS.

Background

Several studies have recently addressed the importance of glycemic variability (GV) in patients with acute coronary syndrome (ACS)[1–4]. Continuous glucose monitoring (CGM) systems are an emerging technology that can continuously measure glucose levels, thereby enabling evaluation of GV[5, 6]. Su et al. reported that monitoring GV using CGM can predict mortality and major adverse cardiovascular events in elderly patients after acute myocardial infarction [7]. They also reported that high GV at admission may be closely correlated with in-hospital poor outcomes in diabetes mellitus (DM) patients with non-ST segment elevation ACS following percutaneous coronary intervention (PCI) [8]. Furthermore, using CGM to monitor daily GV parameters such as mean amplitude of glycemic excursions (MAGE) is a predictor of poor prognosis in patients with ACS without severe DM[9]. In-hospital daily GV in the stable phase of ST-elevation myocardial infarction predicts left ventricular remodeling, as determined by cardiac magnetic resonance imaging[10].

However, the clinical significance of day-to-day GV in patients with ACS remains to be fully elucidated. Therefore, we monitored day-to-day GV in patients with ACS to examine its clinical significance.

Methods

Subjects

We enrolled 25 patients who were admitted to the University of Fukui Hospital with ACS (14 patients with ST-elevated acute myocardial infarction, 6 patients with non-ST elevated acute myocardial infarction, 5 patients with unstable angina) between September 2017 and March 2018. We excluded patients with unstable hemodynamics (use of catecholamines, sedatives, having ventricular arrhythmias, or on ventilator management), patients receiving insulin treatment, and those with an infectious disease.

Smoking was defined as a current or past smoking habit. Diabetes was defined based on one or more of the following: self-reported, use of diabetes medications, fasting plasma glucose ≥ 126 mg/dl, or hemoglobin A1c (National Glycohemoglobin Standardization Program) ≥ 6.5%. Clinical histories of the patients were obtained from interviews with patients' physicians.

Study protocol

After the purpose and methods of the study were explained to patients, they provided written informed consent for participation in the study. In this study, continuous glucose levels were monitored using a flash glucose monitoring FGM) system (Free-Style Libre™ or Free-Style Libre Pro, Abbott™, UK). All patients were implanted with sensors of Free-Style Libre™ or Free-Style Libre Pro™ in their left upper arm within a few days after hospitalization. Glucose levels were recorded using the FGM system for up to 14 days, excluding the first 2 days after sensor implantation because of the risk of errors due to inflammatory reactions, which could produce unstable glucose data. After analysis of the CGM data, MAGE, MODD, ADRR (average daily risk range, mg/dl), J-index, M-value (mg/dl), LBGI (low blood glucose index), and HBGI (high blood glucose index) were calculated using a dedicated program. According to a report by Molar et al., who proposed MODD, the MODD of non-diabetic patients is 6.2 to 8.2 mg/dl[11]. Therefore, we defined a MODD value of ≥ 10 as an outlier. To assess cardiac function, patients underwent echocardiography in the acute and chronic phases. This investigation conformed to the principles outlined in the 1975 Declaration of Helsinki and later amendments. Ethics committee approval and informed consent from all patients were obtained, and the follow-up results were registered in the Universal Hospital Medical Information Network Clinical Trials Registry (UMIN 000023837).

Measurements of blood samples

Within 4 days after hospitalization, following overnight fasting, blood samples were collected from the peripheral vein of each patient and kept on ice. Plasma was collected with EDTA-2Na as an anti-coagulant, and serum samples were separated by centrifugation within 30 min. Blood parameters were determined using standard methods.

Statistical analysis

All statistical analyses were performed using statcel2 and Exel2019. Data are presented as frequencies and percentages for categorical variables and mean ± SD for continuously distributed variables.

Differences between categorical variables were assessed using the χ^2 test. Correlations between continuous variables were determined using Pearson's correlation coefficient test. A p value of < 0.05 was considered statistically significant.

Results

Patient characteristics

The characteristics of all patients are listed in Table 1. The mean age was 69.7 years, and 84% of patients were male. The study included 25 patients (14 patients with ST-elevated acute myocardial infarction, 6 patients with non–ST-elevated acute myocardial infarction, and 5 patients with unstable angina). In the study, 72% had a medical history of hypertension, and 24% had hypercholesterolemia. DM was observed in 8 patients (32%), and 7 patients (28%) were taking one or more antidiabetes medications. The mean value of peak CK was 1310.1 ± 1293.0 U/l, and NT-pro BNP was 2032.0 ± 2063.3 pg/ml (Table 1).

Table 1
Patients' characteristics

characteristics	n = 25
Age (years)	69.7 ± 10.9
Males	21 (84.0)
Risk factor	
DM, (%)	8 (32)
Smoking, (%)	17 (68.0)
BMI (kg/m2)	23.1 ± 3.31
HT, (%)	18 (72)
Previous CAD, (%)	2 (8)
CKD, (%)	11 (44)
DLP, (%)	6 (24)
Medications	
Antiplatelet drug, (%)	5 (20)
Beta-blocker, (%)	1 (4)
ACE-I, ARB, (%)	11(44)
CCB, (%)	10 (40)
statin, (%)	6 (24)
Antihyperuricemic drug, (%)	3 (12)
Oral anti-hyperglycemic drug, (%)	7 (28)
Blood test	
TG, mg/dl	103.7 ± 54.0
LDL, mg/dl	98.32 ± 36.3
HDL, mg/dl	44.6 ± 9.7

AA, arachidonic acid; ACE-I, angiotensin-converting-enzyme; 1–5 AG, 1–5 anhydroglucitol; apoA-Ⅰ, apolipoprotein A-Ⅰ; apoB, apolipoprotein B; apoE, apolipoprotein E; ARB, angiotensin Ⅱ receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCB, Calcium channel blocker; CK, creatine kinase; CKD, chronic kidney disease; DHA, docosahexaenoic acid; DHLA, dihydro gammalinolenic acid; DLP, dyslipidemia; DM, diabetes mellitus; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HT, hypertention; LDL, low-density lipoprotein; MDA-LDL, malondialdehyde-modified low-density lipoprotein; NT-pro BNP, N-terminal pro-brain natriuretic peptide; STEMI, ST segment elevated myocardial infarction; TG, triglyceride; UAP, unstable angina pectoris

characteristics	n = 25
1-5AG, μg/ml	16.7 ± 8.6
apoA-Ⅰ, mg/dl	105.2 ± 16.5
apoB, mg/dl	75.3 ± 23.1
apoE, mg/dl	2.8 ± 0.85
DHLA, μg/ml	33.7 ± 12.1
AA, μg/ml	166.6 ± 41.8
EPA, μg/ml	58.5 ± 42.4
DHA, μg/ml	119.3 ± 48.3
EPA/AA	0.35 ± 0.22
NT-pro BNP, pg/ml	2032.0 ± 2063.3
MDA-LDL, U/l	80.3 ± 29.6
peakCK, U/l	1310.1 ± 1293.0
HbA1c, %	6.23 ± 0.70
Type of ACS	
STEMI, (%)	14 (56)
non-STEMI, (%)	6 (24)
UAP, (%)	5 (20)

AA, arachidonic acid; ACE-I, angiotensin-converting-enzyme; 1–5 AG, 1–5 anhydroglucitol; apoA-Ⅰ, apolipoprotein A-Ⅰ; apoB, apolipoprotein B; apoE, apolipoprotein E; ARB, angiotensin Ⅱ receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCB, Calcium channel blocker; CK, creatine kinase; CKD, chronic kidney disease; DHA, docosahexaenoic acid; DHLA, dihydro gammalinolenic acid; DLP, dyslipidemia; DM, diabetes mellitus; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HT, hypertention; LDL, low-density lipoprotein; MDA-LDL, malondialdehyde-modified low-density lipoprotein; NT-pro BNP, N-terminal pro-brain natriuretic peptide; STEMI, ST segment elevated myocardial infarction; TG, triglyceride; UAP, unstable angina pectoris

Prevalence of MODD and DM

On admission, only 8 patients (32%) were diagnosed with diabetes. On the other hand, as many as 24 of 25 patients (96%) had abnormally high MODD values. The rate of abnormal MODD was significantly higher than the diagnosed rate of DM (32% vs 96%, $p < 0.001$) (Fig. 1).

Correlation of MODD and NT-pro BNP

MODD was correlated with MAGE, J-index, and M-value (mg/dl), which are indicators of GV. MODD was also correlated with LBGI, HBGI, and ADRR, which is another indicator of day-to-day GV. There was no correlation between MODD and lipid-related coronary risk factors such as LDL, apoB, and EPA/AA (Table 2).

Table 2
Single correlation analysis between MODD and clinical characteristics, other indices of blood glucose fluctuation

	R	P
MAGE (mg/dl)	0.85	< 0.001
ADRR (mg/dl)	0.86	< 0.001
M-value (mg/dl)	-0.08	0.7
J-index	0.83	< 0.001
LBGI	-0.24	0.24
HBGI	0.85	< 0.001
HbA1c (%)	0.47	0.019
1-5AG (μg/ml)	-0.22	0.3
TG (mg/dl)	-0.19	0.35
LDL (mg/dl)	-0.0096	0.96
HDL (mg/dl)	-0.19	0.37
apoA-Ⅰ (mg/dl)	-0.38	0.063
apoB (mg/dl)	0.054	0.8
apoE (mg/dl)	-0.011	0.96
DHLA (μg/ml)	-0.23	0.27
AA (μg/ml)	0.15	0.46
EPA (μg/ml)	-0.0082	0.97
DHA (μg/ml)	-0.12	0.56
EPA/AA	-0.072	0.73
MDA-LDL (U/l)	-0.023	0.91
NT-pro BNP (pg/ml)	0.41	0.042
maxCK (U/l)	0.25	0.23

ADRR, average daily risk range; AA, arachidonic acid; apoA-Ⅰ, apolipoprotein A-Ⅰ; apoB, apolipoprotein B; apoE, apolipoprotein E; CK, creatine kinase; DHA, docosahexaenoic acid; DHLA, dihydro gammalinolenic acid; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; HBGI, hugh blood glucose index; HDL, high-density lipoprotein cholesterol; LBGI, low blood glucose index; LDL, low-density lipoprotein; MAGE, mean amplitude of glycemic excursions; MDA-LDL, malondialdehyde-modified low-density lipoprotein; NT-pro BNP, N-terminal pro-brain natriuretic peptide; TG, triglyceride

A positive correlation was found between MODD and NT-pro BNP ($r = 0.409$, $p = 0.042$). Although MODD did not correlate with max CK, there was a positive correlation between MODD and NT-pro BNP ($r = 0.41$, $p = 0.042$, respectively) (Table 2, Fig. 2).

Discussion

The main findings of the present study were as follows. First, among 25 patients with ACS, the prevalence of abnormal MODD was high (96%) compared to the prevalence of DM (38%). Second, there was a correlation between MODD, a parameter of day-to-day GV, and NT-pro BNP, a parameter of cardiac function.

In the present study, 8 patients (32%) were diagnosed with diabetes at or before admission to the hospital. In contrast, MODD assessed by CGM was found to be over the normal level (> 10) in 24 (96%) patients. These results suggest that CGM may provide indications of diabetes and glucose intolerance in some patients who were considered normal using previous diagnostic methods. Previous reports have shown that when oral glucose tolerance testing (OGTT) was performed on patients admitted with ACS, 24% were diagnosed as diabetic, 38% as impaired glucose tolerance, and the remaining 38% as normal[12, 13]. Day-to-day assessment of blood glucose using CGM could identify patients with blood glucose variations beyond daily glucose variability.

We also found that a large number of ACS patients had GV, suggesting that blood glucose variability causes plaque instability and endothelial erosion, which may be a trigger for ACS. This is supported by a previous report that higher blood glucose variability is an important factor in coronary plaque vulnerability[14, 15].

Although day-to-day GV in the acute phase may differ from day-to-day variability in regular outpatient care, it was suggested that incorporating CGM into routine diabetes care and measuring MODD may help to differentiate patients at high risk for ACS who are being impacted by GV.

We also examined the association between MODD and other indices. Despite the lack of correlation between peak CK and MODD, MODD was found to be associated with NT-pro BNP. MOD was not correlated with CK, which reflects the degree of myocardial infarction. In addition, there was no correlation between infarct size and MODD. On the other hand, the fact that MODD was correlated with NT-pro BNP, a marker of cardiac function, suggests the presence of prior myocardial dysfunction in addition to the myocardial infarction that caused the patient to be hospitalized. These results are not inconsistent with previous reports that daily and day-to-day GV increase oxidative stress and inflammation, which cause myocardial damage[16–19]. Recent investigations suggest that α-glucosidase inhibitor and glucagon-like peptide-1 analogue attenuate GV and inhibit oxidative injury[20, 21]. Therefore, we could improve prognosis using these drugs.

Clinical implications

The significance of measuring MODD in patients with ACS is that the measurement can predict more heart failure symptoms beyond those expected based on infarct volume and may serve as a marker for more-intensive anti-cardiac therapy. In addition, CGM in DM routine practice may help in risk stratification of vulnerable patients with ACS.

Limitations

Although some of the patients in this study had high HbA1c levels, these patients may have had less blood glucose variability and been less likely to have MODD abnormalities and therefore should have been omitted from the study, we included them due to the limited number of cases. Therefore, the correlation between MODD and NT-pro BNP in this study may be weak. In addition, OGTT was not used to diagnose diabetes at hospitalization. This may have resulted in a lower rate of diabetes diagnosis. However, the rate of elevated MODD was higher than the number of diagnoses of DM comorbidities and new DM cases on admission for ACS previously reported.

Conclusions

In conclusion, CGM estimations of MODD, a parameter of day-to-day GV, in ACS patients were abnormal at a high rate. In ACS patients, there was a correlation between MODD and NT-pro BNP, a parameter of cardiac function. Evaluating MODD in ACS patients may therefore be useful for assessing aggravation of heart failure damage.

Abbreviations

ACS: acute coronary syndrome; ADRR: average daily risk range; CGM: continuous glucose monitoring; DM: diabetes mellitus; FGM: flash glucose monitoring GV: glycemic variability; HBGI: high blood glucose index; LBGI: low blood glucose index; MAGE: mean amplitude of glycemic excursions; MODD: mean of daily differences; NT-pro BNP: N-terminal pro-brain natriuretic peptide; OGTT: oral glucose tolerance testing PCI: percutaneous coronary intervention

Declarations

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Author's contributions: Machiko Miyoshi collected and analyzed data and wrote the manuscript. Hiroyasu Uzui contributed to conceptualization, investigation, and critical revision. Tomohiro Shimizu, Takayoshi Aiki, Yuichiro Shiomi, Minoru Nodera, Hiroyuki Ikeda, Naoto Tama, Kanae Hasegawa, Kentaro Ishida, Shinsuke Miyazaki contributed to data curtion. Tetsuji Morishita contributed to data curation and formal analysis. Hiroshi Tada contributed to supervision.

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Figures

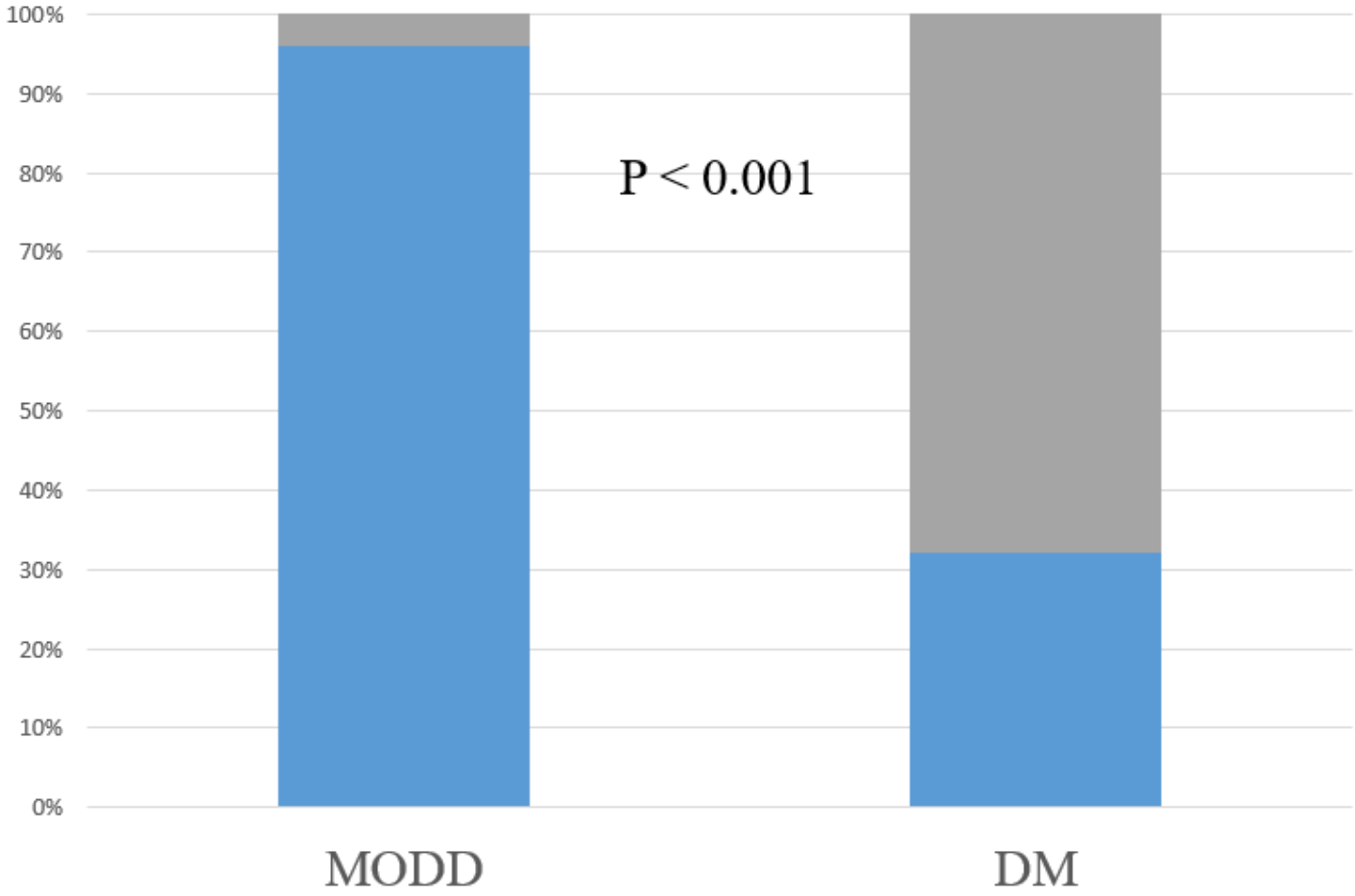

Figure 1

Prevalence of MODD and DM. Detection rate of MODD abnormalities was significantly higher than the diagnosed rate of DM (32% vs 96%, p<0.001). DM, diabetes mellitus; MODD, mean of daily differences

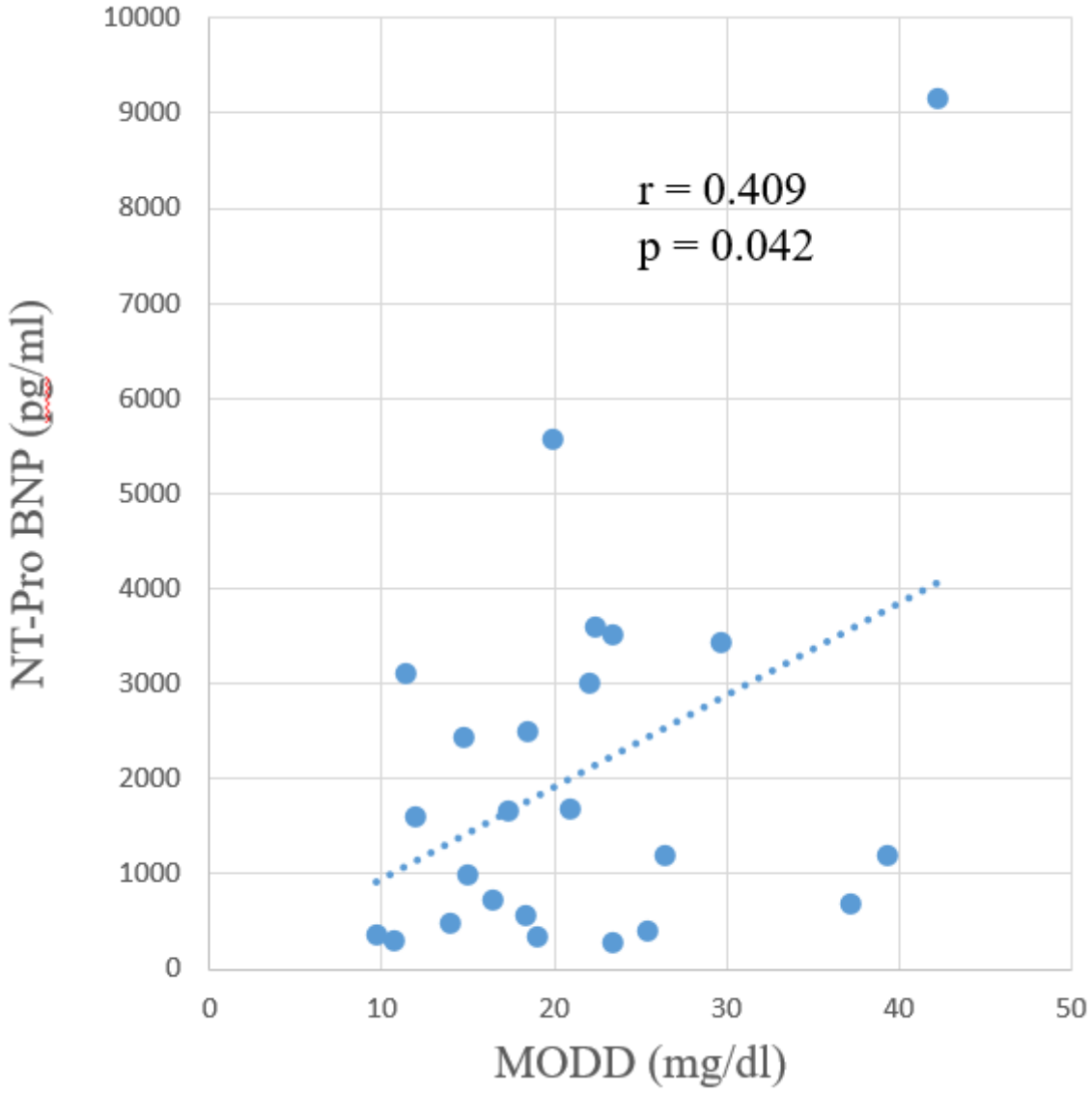

Figure 2

Correlation between MODD and NT-proBNP. A positive correlation was found between MODD and NT-proBNP (r=0.409, p=0.042). MODD, mean of daily differences; NT-proBNP, N-terminal pro–brain natriuretic peptide