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ORIGINAL ARTICLE

History of gastroesophageal reflux disease in patients with suspected coronary artery disease

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Abstract

It is well known that patients with gastroesophageal reflux disease (GERD) experience GERD-related chest pain, but little is known about the relationship between GERD and coronary artery disease (CAD). We evaluated medical history of GERD in patients with suspected CAD and its association with types of CAD. We enrolled 236 patients who underwent coronary angiography (CAG). We assessed past medical history of each patient, making note of esophageal or stomach diseases such as GERD including reflux esophagitis and non-erosive reflux disease. The patients were divided into the following three subgroups based on the CAG results. Group I, patients with o-CAD (> 50% stenosis with ischemic findings, $n = 141$); Group II, patients with vasospastic angina (VSA, with positive spasm provocation test without organic coronary stenosis, $n = 52$); and Group III, patients without organic coronary stenosis or VSA ($n = 43$). Group I included more men than women ($p < 0.001$) and the frequencies of smoking, lipid disorders, and diabetes mellitus in this group were higher than those in the other groups ($p < 0.01$). The frequency of medical history of GERD was significantly higher in Group II (21%) than in Group I (3%) or Group III (7%, $p < 0.0001$). Logistic regression analysis showed that a medical history of GERD (OR 7.8; $p < 0.01$) was one of the factors associated with the presence of VSA. Our findings showed that a medical history of GERD was frequently observed in approximately one-fifth of patients with VSA, indicating that VSA may be present in patients with chest pain and a medical history of GERD.

Keywords Acetylcholine · Coronary artery disease · Non-erosive gastroesophageal reflux disease · Non-cardiac chest pain · Vasospastic angina

Introduction

The causes of chest pain may include chest wall-related problems, cardiac causes, pulmonary causes, gastrointestinal causes, or psychogenic and/or psychosomatic causes. Among cardiac causes, coronary artery disease (CAD) is thought to be common and cardiologists should first consider it in diagnosing cardiac origin chest pain. However, the chest symptoms of CAD vary based on the type of onset (acute or stable coronary syndrome) or the presence of vasospastic angina (VSA) [1]. Thus, even in patients with CAD, we have often encountered some patients whose chest symptoms could not be easily distinguished. On the other hand, in cases of non-cardiac chest pain (NCCP), gastroesophageal reflux disease (GERD) has been found to be the main cause [2, 3]. It is well known that patients with GERD have GERD-related chest pain as an extra-esophageal symptom, which usually occurs after meals but also during the night, sometimes mimicking angina pectoris [4, 5].

Thus, there may be some shared symptoms between GERD and CAD, especially VSA; however, little is known regarding the associations between them. Therefore, we evaluated medical history of GERD in patients with suspected CAD and further, whether such history differs based on the type of CAD.

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Methods

Study patients

In the present observational study, we enrolled 236 patients (median age, 67 years; 155 males) who underwent coronary angiography (CAG) for the first time during CAD evaluation. We excluded patients who underwent CAG for assessment of cardiac diseases other than CAD such as moderate to severe valvular heart disease, heart failure not due to CAD, or cardiomyopathies including hypertrophic cardiomyopathy. We also excluded patients with moderate to severe chronic kidney disease (estimated glomerular filtration ratio < 45 mL/min/1.73 m^2). The study protocol was approved by the Ethics Committee of our institution, and written informed consent was obtained from all patients.

Coronary angiography (CAG) and spasm provocation test (SPT)

All medications were continued in patients who had documented coronary stenosis identified via cardiac computed tomography (CT), positive ischemic findings identified via exercise stress electrocardiograms (ECG) or pharmacological stress myocardial perfusion imaging, or typical ischemic chest symptoms during exercise. A diagnostic CAG was performed using 4-French gage (4-Fr) or 5-Fr Judkins diagnostic catheters via a radial artery approach or a brachial artery approach. Immediately after insertion of the sheath, 200 μg of nitroglycerin (NTG) was infused intravenously. Angiograms were obtained from multiple projections using an autoinjector (ZoneMaster, Sheen Man, Osaka) to inject 5 mL contrast medium at 2.5 mL/s. If a moderate atherosclerotic lesion was recognized in angiograms, we measured the fractional flow reserve (FFR) after intravenous infusion of adenosine triphosphate to assess the organic stenosis functionality using a pressure wire (PrimeWire Prestige Plus Guide Wire or Verrata Pressure Guide Wire, Phillips Volcano Therapeutics Inc., Rancho Cordova, CA, United States).

In cases of patients with suspected VSA or with chest symptoms at rest alone or both at rest and during exercise, all antianginal agents were discontinued at least 48 h before catheterization except for sublingual nitroglycerin (NTG), which was only withheld beginning 1 h before catheterization. We performed an SPT after standard diagnostic CAG using the percutaneous brachial approach. A 5-Fr transient pacing catheter (Bipolar Balloon Catheter, Bebrawn, Melsungen, Germany) was inserted into the right ventricle via the internal jugular vein or medial cubital vein and set at 50 beats/min. Arterial pressure, heart rate, and ECG readings were monitored continuously and recorded using a multichannel recorder (Polygraph 1600, Nihon Electric Corporation, Tokyo, Japan).

The methodology of routine SPT has been previously described [6, 7]. In brief, after initial CAG, 30-μg or 50-μg dose of acetylcholine (ACh) was infused into the right coronary artery (RCA) for 20 s, with 3-min intervals between consecutive doses. If coronary spasms were not induced due to 50 μg of ACh, a maximum dose of 80 μg was infused into the RCA. CAG was performed immediately after coronary spasms were induced or the maximum ACh infusion was completed. After spasm provocation in the RCA, we infused 50-μg or 100-μg dose of ACh into the left coronary artery (LCA) for 20 s, with 3-min intervals between doses. If coronary spasms were not induced due to 100 μg of ACh, a maximum of 200 μg ACh was infused into the LCA, with or without 20, 40, or 60 μg of ergometrine maleate. CAG was performed immediately after coronary spasms were induced or the maximum ACh infusion was completed. After intracoronary injections of 200 μg NTG, we performed the final CAG of the LCA.

The method for measuring coronary artery diameter has been described previously [8]. We selected spastic and atherosclerotic segments for quantitative analysis. In all cases, the luminal diameters were measured by a single investigator who was blinded to the clinical data, using an end-diastolic frame in a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR; Siemens, Berlin, Germany). Measurements were performed three times and the average value was used for analysis. Changes in coronary artery diameter in response to ACh and NTG infusions were represented as percentage changes from baseline angiographic measurements. The intra- and inter-observer validity of this method have been reported to be excellent [9].

A percent stenosis value > 50% and/or an FFR value ≦0.8 were interpreted as organic stenosis. VSA was defined as > 90% narrowing of the epicardial coronary arteries found via angiography during SPT, the presence of characteristic chest pain, and/or the presence of ST-segment deviation identified via ECG [1].

Group classifications

Based on the results of CAG and SPT, the patients were divided into the following three groups. Group I consisted of 141 patients with organic stenosis (stenosis > 50%) identified via CAG accompanied only by typical ischemic symptoms ($n = 42$) or with positive results in examinations for myocardial ischemia such as exercise stress ECG ($n = 40$), cardiac CT ($n = 32$) or pharmacological stress myocardial perfusion imaging ($n = 27$). Group II consisted of 52 patients with positive SPT outcome but without organic stenosis. Group

III consisted of 43 patients with neither organic stenosis nor positive SPT outcome.

History of gastroesophageal disease and medications

We assessed past medical history of each patient, making note of esophageal or stomach diseases. Diagnosis of peptic ulcers (PU) and GERD were made via self-assessment based on information from patients and their families ($n=132$) and by extracting information from letters of introduction ($n=23$) and medical records at our institution ($n=81$). We confirmed previous upper gastrointestinal endoscopy in approximately 70% of the patients. GERD cases included erosive esophagitis and non-erosive reflux disease (NERD). We recorded details of medication such as proton pump inhibitors and H2-receptor blockers, as well as statins, antiplatelet therapy including aspirin, $P2Y_{12}$ inhibitors, dual antiplatelet therapy (DAPT), and vasodilators.

Assessment of biochemical markers and coronary risk factors

Fasting blood samples were obtained on the day of the CAG. We questioned all patients regarding their smoking status and classified them as current smokers, past smokers (those who had stopped smoking for at least one month), or non-smokers. The presence of hypertension was defined based on a systolic blood pressure of ≥ 140 mmHg, a diastolic blood pressure of ≥ 90 mmHg, and/or use of antihypertensive medication. In terms of blood chemical parameters, we measured the levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, fasting blood sugar, hemoglobin A1C, creatinine, C-reactive protein, and brain natriuretic peptide (BNP). The estimated glomerular filtration rate (mL/min/1.73 m^2) was calculated using the standard formula [10] and the presence of chronic kidney disease (CKD) was defined using standard criteria [11]. We calculated low-density lipoprotein cholesterol level using the Friedewald equation [12]. We defined dyslipidemia based on a low-density lipoprotein cholesterol level of ≥ 120 mg/dL and/or the use of medications for the condition. We defined diabetes mellitus based on fasting blood sugar levels of ≥ 126 mg/dL and hemoglobin A1C levels ≥ 6.5%, and/or the use of anti-diabetic medications. The presence of metabolic syndrome (MtS) was also defined based on standard criteria [13]. We also evaluated family history of CAD, and left ventricular ejection fraction (LVEF) via echocardiography. As shown previously [14, 15], flow-mediated dilation (FMD) and NTG-induced dilation (NID) of the brachial artery were assessed using the UNEXEF device (UNEX Corp, Nagoya, Japan), representing endothelium-dependent and endothelium-nondependent functions, respectively.

Assessment of chest symptoms in VSA patients

In VSA patients (Group II), chest symptoms including frequency of chest symptoms (number/month), duration of disease (months), response to sublingual NTG, and time of occurrence of chest symptoms (midnight, early morning, or daytime) were assessed depending on the presence of GERD.

Statistical analysis

Data are represented as mean ± SD. Median with interquartile ranges were used to represent non-normally distributed data or non-continuous variables. Baseline characteristics of the three groups and of subgroups in Group II were compared using Student's unpaired *t* test, Wilcoxon signed-rank test, or χ^2 analysis, as appropriate. Logistic regression analysis was used for determining the factors associated with the presence of VSA, using p value < 0.05 as a threshold. All statistical analyses were performed using JMP Ver. 12 (SAS Institute Inc., USA). A p value < 0.05 was considered statistically significant.

Results

Patient characteristics

There were 141 patients in Group I, 52 patients in Group II, and 43 patients in Group III. The patient characteristics in the three groups are shown in Table 1. Presence of the male gender was significantly higher in Group I than in the other two groups ($p < 0.0001$), while age and body mass index

Table 1 Patients' characteristics

	Group I	Group II	Group III	*p* value
No.	141	52	43	
Age (years)	68 ± 11	67 ± 11	66 ± 11	NS
M/F	108/33	24/28	23/20	< 0.0001
Body mass index	24.0 ± 4.0	24.7 ± 4.5	24.8 ± 3.9	NS
Coronary risk factors (%)				
Smoking	94 (67)	22 (42)	24 (56)	0.0377
Current/past	26/68	14/8	17/7	
Hypertension	92 (65)	31 (60)	34 (79)	NS
Dyslipidemia	109 (77)	31 (60)	22 (51)	0.0017
Diabetes mellitus	64 (45)	14 (27)	10 (23)	0.0068
Family history of CAD	20 (14)	12 (23)	9 (21)	NS
MtS (%)	61 (43)	15 (29)	12 (28)	0.0657
CKD (%)	72 (51)	20 (38)	17 (49)	NS

CAD coronary artery disease, *CKD* chronic kidney disease, *MtS* metabolic syndrome, *NS* not significant

were not different among the three groups. In terms of conventional coronary risk factors, the presence of hypertension did not differ among the three groups; however, smoking ($p=0.037$), dyslipidemia ($p=0.0017$), and diabetes mellitus ($p=0.0068$) were significantly higher in Group I than in the other two groups. Family history of CAD did not differ among the three groups. The presence of MtS tended to be higher in Group I than in the other two groups ($p=0.0657$). The presence of CKD did not differ among the three groups.

Blood chemical and ultrasonographic parameters

The results of blood chemical and ultrasonographic parameters are shown in Table 2. Triglyceride level ($p=0.0006$), fasting blood sugar level ($p=0.0023$), hemoglobin A1C level ($p=0.0021$), and metabolic score (<0.0001) were higher and high-density lipoprotein cholesterol level ($p=0.0006$) and eGFR (0.0073) were lower in Group I than in other two groups. The level of BNP was lower in Group II than in Group I ($p=0.0038$).

LVEF assessed via echocardiography was lower in Group I than in the other two groups ($p=0.0079$). Brachial ultrasonography showed that FMD was lower in Group I and tended to be lower in Group II than in Group III ($p=0.0479$), and NID was significantly lower in Group I than in the other two groups ($p=0.0042$).

Medications

Medication usage is shown in Table 3. Statin usage was significantly higher in Group I than in the other two groups ($p<0.0001$). Use of vasodilators including nitroglycerin and calcium channel blockers (CCB) was significantly higher in Groups I and II than in Group III. Use of antiplatelet therapy was higher in Group I than in the other two groups and the median number of antiplatelet drugs was also higher in Group I than in the other two groups. Use of stomach medications was more frequently observed in Groups I and II than in Group III ($p<0.0001$) and the median number of stomach medications was higher in Group I than in other two groups ($p<0.0001$). In Group I, the number of stomach medications was associated with that of antiplatelet drugs ($p<0.0001$); however, in Groups II and III, no such association was present.

The frequencies of GERD and peptic ulcer

The frequency of GERD was significantly higher in Group II than in the other two groups ($p<0.0001$), while the medical history of peptic ulcer was not different among the three groups (Fig. 1). The frequencies of CCB or nitrate use were not associated with the frequency of GERD. Based on the above findings, we performed subsequent analyses to identify factors associated with the presence of VSA.

Logistic regression analyses showed that a medical history of GERD as well as low log BNP level, female gender, absence of HL, and reduced FMD were significant factors associated with the presence of VSA (Table 4).

Table 2 Blood chemical parameters and ultrasonographic parameters

	Group I	Group II	Group III	*p* value
Blood chemical parameters				
Total cholesterol (mg/dL)	189 ± 38	188 ± 34	185 ± 28	NS
Triglyceride (mg/dL)	144 ± 79	118 ± 38	102 ± 39	0.0006
HDL cholesterol (mg/dL)	53 ± 15	60 ± 16	61 ± 16	0.0006
LDL cholesterol (mg/dL)	100 ± 34	104 ± 31	103 ± 31	NS
Fasting blood glucose (mg/dL)	112 ± 29	104 ± 17	98 ± 11	0.0023
Hemoglobin A1C (%)	6.5 ± 1.3	6.0 ± 0.7	5.9 ± 1.1	0.0021
eGFR (mL/min/1.73 m^2)	65.8 ± 16.3	71.1 ± 16.6	73.8 ± 13.2	0.0073
C-reactive protein (mg/dL)	0.26 ± 0.50	0.14 ± 0.24	0.21 ± 0.48	NS
BNP (pg/mL)	41 (18, 90)	22 (14, 37)	27 (10, 88)	0.0038
Log BNP	1.65 ± 0.51	1.39 ± 0.41	1.51 ± 0.56	0.0035
Ultrasonographic parameters				
LVEF (%)	61 ± 12	67 ± 13	65 ± 12	0.0079
FMD (%)	3.2 ± 3.4	3.4 ± 3.8	4.7 ± 3.8	0.0479
NID (%)	12.3 ± 5.8	15.3 ± 6.8	16.2 ± 6.3	0.0042

BNP brain natriuretic peptide, *FMD* flow-mediated dilation, *eGFR* estimated glomerular filtration ratio, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LVEF* left ventricular ejection fraction, *NID* nitroglycerin-induced dilation, *NS* not significant

Table 3 Medications

	Group I	Group II	Group III	*p* value
Statin (%)	93 (66)	20 (39)	11 (26)	< 0.0001
Nitrates (%)	26 (18)	12 (23)	0 (0)	0.0048
Calcium channel blocker (%)	49 (35)	22 (42)	17 (40)	NS
Anti-platelet therapy (%)	129 (91)	19 (37)	12 (28)	< 0.0001
No. of anti-platelet therapy	2 (1, 2)	0 (0, 1)	0 (0, 1)	< 0.0001
Aspirin (%)	116 (82)	13 (25)	12 (28)	< 0.0001
$P2Y_{12}$ inhibitor (%)	111 (79)	10 (19)	5 (12)	< 0.0001
DAPT (%)	100 (71)	7 (13)	5 (12)	< 0.0001
Stomach medication (%)	116 (82)	27 (52)	14 (32)	< 0.0001
Proton pump inhibitor (%)	88 (62)	25 (48)	11 (28)	< 0.0001
Histamine2 receptor antagonist (%)	19 (13)	1 (2)	2 (5)	0.0253
Other (%)	20 (14)	12 (23)	3 (7)	0.0843
No. of stomach medications (%)	1 (1, 1)	1 (0, 1)	0 (0, 1)	< 0.0001

DAPT dual antiplatelet therapy, *No.* number, *NS* not significant

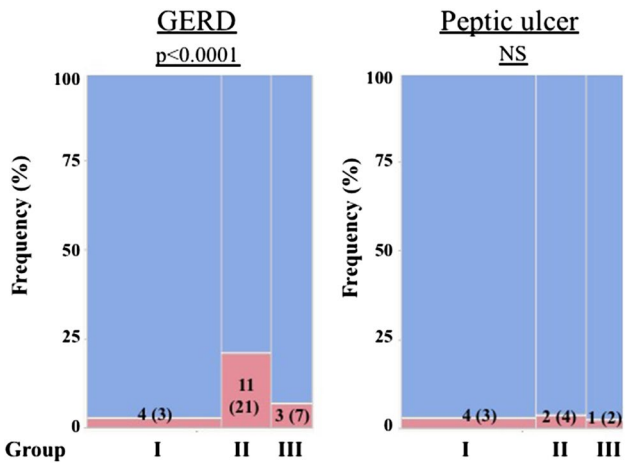

Fig. 1 Medical history of peptic ulcer and gastroesophageal reflux disease. (*GERD* gastroesophageal reflux disease, *NS* not significant)

Table 4 Logistic regression analyses of presence of vasospastic angina

Factors	Presence of VSA	
	Odds ratio	*p* value
Low level of Log BNP	13.17	0.0003
Female sex	8.17	0.0043
Presence of GERD	7.81	0.0052
Absence of dyslipidemia	5.05	0.0246
FMD	5.01	0.0253
		$R^2 = 0.1338$

BNP brain natriuretic peptide, *FMD* flow-mediated dilation, *GERD* gastroesophageal reflux disease, *VSA* vasospastic angina

Clinical characteristics and chest symptoms in Group II

In Group II, medical history of GERD was more frequently observed in women (32%) than in men (8%, $p = 0.0361$). Based on the medical history of GERD, chest symptoms were assessed. The median number of chest symptoms per month was not different (GERD −, 4/month; GERD +, 8/month; ns) but the median duration of disease tended to be longer in VSA patients with GERD (48 months) than in VSA patients without GERD (3 months; $p = 0.0781$). Response to sublingual NTG was confirmed in 18 (44%) of 41 patients without GERD and in 4 (36%) of 11 patients with GERD. Among them, sublingual NTG was used in all patients without GERD (100%) and in 3 of 4 patients with GERD (75%, $p = 0.0299$). The time of occurrence of chest symptoms between the two groups was similar (GERD +, 27% at midnight, 27% in the early morning, 45% during daytime; GERD −, 29% at midnight, 17% in the early morning, 54% during daytime; ns). A representative case from Group II with GERD is shown in Fig. 2.

Discussion

In the present study, we evaluated medical history of GERD in patients who underwent CAD. We found that the presence of GERD was significantly higher in patients with VSA than in patients with organic CAD or in patients without organic CAD or VSA. Further, we found that medical history of GERD was one of factors associated with the presence of VSA. Thus, the present study suggests an association between GERD and VSA.

To diagnose CAD, it is important to obtain details of the patients' present illness [1, 16]; however, we have

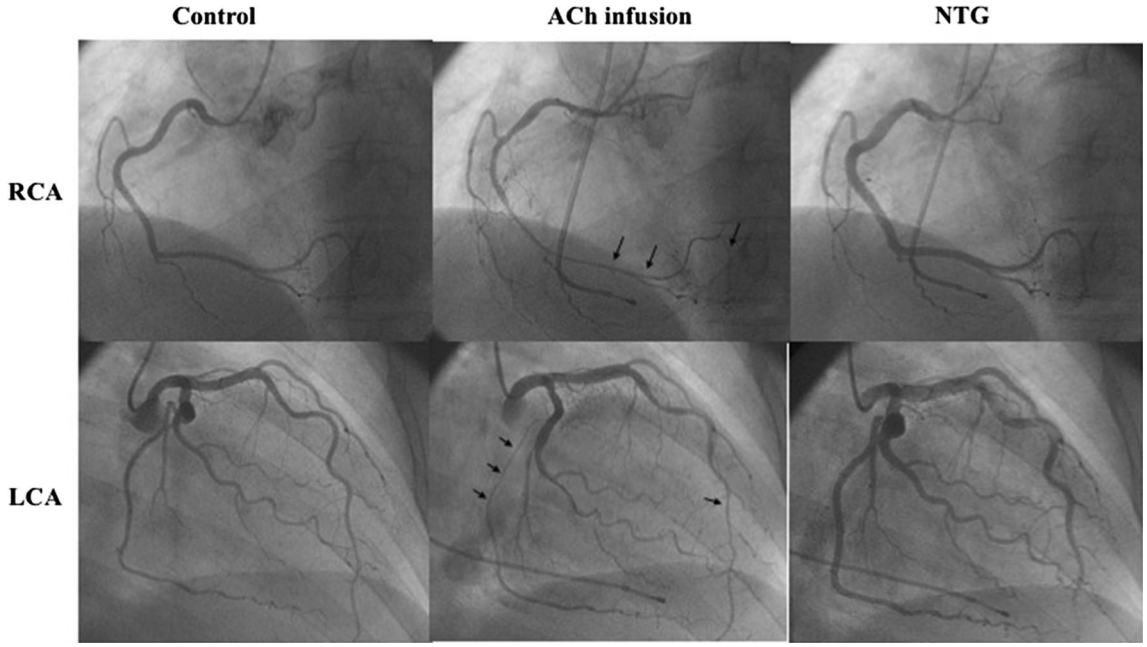

Fig. 2 A representative case from Group II with GERD. A woman in her fifties had chest discomfort at rest for 2 years. She visited a hospital and underwent coronary computed tomography, which showed no significant coronary stenosis. Thereafter, she underwent upper gastrointestinal endoscopy and she was diagnosed with non-erosive reflux disease. She had taken a proton pump inhibitor and mosapride, but her symptoms had continued. She was referred to our hospital due to possible coronary spasm and underwent coronary angiography and spasm provocation test. Initial coronary angiograms showed no significant coronary stenosis (right upper and lower panels). Infusion of ACh caused coronary spasm in the RCA with the usual chest pain (middle upper panel). Intracoronary NTG was administered into the RCA and the coronary artery dilated well (left upper panel). Then, another infusion of ACh into the LCA caused multiple spasms at the LCX and LAD (middle lower panel). Intracoronary NTG injection into the LCA was repeated and the coronary dilated well (left lower panel). Spasms are indicated by arrows. *RCA* right coronary artery, *LCA* left coronary artery, *ACh* acetylcholine, *NTG* nitroglycerin, *LCX* left circumflex coronary artery, *LAD* left anterior descending coronary artery

occasionally encountered patients whose symptoms were difficult to distinguish between cardiac chest pain and NCCP. Among NCCP cases, GERD has been found to be the main causative factor [2, 3, 17–19]. It is well known that GERD-related chest pains usually occur after meals but also during the night, sometimes mimicking angina pectoris [4, 5]. In patients with GERD, it has been reported that NERD has often been medically refractory to standard therapy compared with patients with erosive esophagitis [20–23]. Asaoka et al. [23] reported that residual symptoms were present in approximately one-third of NERD patients even after administration of potassium-competitive acid blockers. Eslick et al. [24] have shown that the mortality rate due to cardiac death was 5.5% over a 4-year observation period, indicating that some patients with NCCP have potential cardiac abnormalities. Thus, it has been thought that NERD has heterogenous factors or causes [25], and it is possible that patients with CAD, especially those with abnormal coronary function such as VSA, may be present undetected among patients with NCCP or GERD.

There are two possible explanations for the relationship between VSA and GERD found in the present study. One explanation is the misdiagnosis of VSA as GERD. As mentioned above, the symptoms of VSA and GERD are similar. In addition, younger patients and middle-aged female patients have possibilities of VSA [26–28] in the clinical setting; however, these patients or population groups are not usually thought to be candidates for organic coronary stenosis, in general. Our data, showing that female patients were more frequent in Group II with GERD and that the duration of disease tended to be longer in the same group, may support the above explanation. Further, in assessment of chest pain, it is unclear which modalities have been applied to such patients [16, 29]. In the clinical setting, VSA cannot be usually diagnosed using exercise ECG tests or cardiac CT [1] and the presence of VSA using SPT might not have been assessed routinely. Thus, it is possible that we misdiagnosed VSA as GERD or NCCP. Another explanation is the possibility of actualization of GERD-related symptoms due to CCB use as a treatment for VSA. It is well known that CCB use worsens GERD-related symptoms due to the dilation of smooth muscles of the esophagus [30, 31]. Thus, it is possible that the increase in GERD occurrence in VSA patients was only the result of treatment with CCB in such patients. However, in the present study, we showed that CCB use

did not influence medical history of GERD. Therefore, we infer that the former explanation is the likely mechanism responsible for the relationship between GERD and VSA.

There were several limitations to the present study. First, all patients did not always undergo upper gastrointestinal endoscopy or respond to a questionnaire for GERD [32] and the diagnosis of GERD and PU was made based only on information from patients and their families, letters of introduction, and medical records. Thus, the precise diagnosis of GERD or the kinds of GERD (erosive esophagitis or NERD) remained unclear. Further study using both upper gastrointestinal endoscopy and CAG with SPT will be needed to confirm the relationship between types of GERD and VSA. Second, we included patients who underwent CAG because of any chest symptoms and/or positive findings in provocation tests for myocardial ischemia. This indicates that patients who were likely to have CAD were also more likely to be included. Therefore, our findings, especially those regarding the frequency of GERD, may not always have accounted for all outpatients suspected of CAD. Third, we defined VSA as a positive SPT outcome without organic coronary stenosis. However, in practice, there are many patients with both VSA and organic stenosis. Further, many patients with neither organic stenosis nor VSA (Group III) had chest symptoms. Thus, these patients may not always have been normal controls and those with microvascular angina might have been included in Group III. Fourth, assessment of medication use was performed at admission for CAG. At our institution, ad hoc percutaneous coronary intervention has been aggressively performed and the usage of antiplatelet drugs, especially DAPT, might have been high in the present study. Finally, stomach medication use was higher in Group I and we consider this to be due to increased antiplatelet therapy; however, such increased stomach medication use might have decreased GERD occurrence in this group.

In conclusion, the present study showed that a medical history of GERD was more frequently observed in VSA patients than in others, and was seen in approximately one-fifth of VSA patients. Cardiologists should bear in mind that VSA may be present in patients with chest pain and a medical history of GERD, and that such medical history may be an indication to assess VSA. Further, gastroenterologists and general physicians should also bear in mind that VSA may be present undetected among patients with medically refractory GERD or NCCP. Finally, we would like to propose that NCCP should be diagnosed after exclusion of cardiovascular diseases including VSA.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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