




ORIGINAL RESEARCH

Impact of Myocardial Bridge on Life-Threatening Ventricular Arrhythmia in Patients With Implantable Cardioverter Defibrillator

Kozo Okada , MD; Kiyoshi Hibi, MD; Yutaka Ogino, MD; Nobuhiko Maejima, MD; Shinnosuke Kikuchi, MD; Hidekuni Kirigaya, MD; Jin Kirigaya , MD; Ryosuke Sato, MD; Hidefumi Nakahashi, MD; Yugo Minamimoto, MD; Yuichiro Kimura, MD; Eiichi Akiyama, MD; Yasushi Matsuzawa, MD; Noriaki Iwahashi , MD; Masami Kosuge, MD; Toshiaki Ebina, MD; Kouichi Tamura, MD; Kazuo Kimura, MD

BACKGROUND: Myocardial bridge (MB), common anatomic variant, is generally considered benign, while previous studies have shown associations between MB and various cardiovascular pathologies. This study aimed to investigate for the first time possible impact of MB on long-term outcomes in patients with implantable cardioverter defibrillator, focusing on life-threatening ventricular arrhythmia (LTVA).

METHODS AND RESULTS: This retrospective analysis included 140 patients with implantable cardioverter defibrillator implantation for primary (n=23) or secondary (n=117) prevention of sudden cardiac death. Angiographically apparent MB was identified on coronary angiography as systolic milking appearance with significant arterial compression. The primary end point was the first episode(s) of LTVA defined as appropriate implantable cardioverter defibrillator treatments (antitachyarrhythmia pacing and/or shock) or sudden cardiac death, assessed for a median of 4.5 (2.2–7.1) years. During the follow-up period, LTVA occurred in 37.9% of patients. Angiographically apparent MB was present in 22.1% of patients; this group showed younger age, lower rates of coronary risk factors and ischemic cardiomyopathy, higher prevalence of vasospastic angina and greater left ventricular ejection fraction compared with those without. Despite its lower risk profiles above, Kaplan–Meier analysis revealed significantly lower event-free rates in patients with versus without angiographically apparent MB. In multivariate analysis, presence of angiographically apparent MB was independently associated with LTVA (hazard ratio, 4.24; 95% CI, 2.39–7.55; $P<0.0001$).

CONCLUSIONS: Angiographically apparent MB was the independent determinant of LTVA in patients with implantable cardioverter defibrillator. Although further studies will need to confirm our findings, assessment of MB appears to enhance identification of high-risk patients who may benefit from closer follow-up and targeted therapies.

Key Words: lethal ventricular arrhythmia ■ myocardial bridging ■ sudden cardiac death

Myocardial bridge (MB) is a common congenital coronary anomaly that predominantly involves the mid to distal segments of the left anterior descending (LAD) artery and constricts the bridged coronary segment during systole.^{1–5} MB is generally considered benign, because coronary blood flow in the LAD primarily occurs during diastole, and most patients with MB are indeed presumed asymptomatic,

whereas many studies suggested a potential hemodynamic significance of MB in certain patient subsets and some, usually case reports, implied a possible relationship between MB and various cardiovascular pathologies,^{1–5} including myocardial ischemia,^{6–8} endothelial dysfunction and vasospastic angina (VSA),^{9–12} acute coronary syndromes,^{13,14} left ventricular (LV) dysfunction,^{15,16} certain types of cardiomyopathy,²

Correspondence to: Kozo Okada, MD, Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan. E-mail: kokada2@yokohama-cu.ac.jp
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CLINICAL PERSPECTIVE

What Is New?

- Among patients treated with implantable cardioverter defibrillator for primary or secondary prevention of sudden cardiac death, angiographically apparent myocardial bridge (MB) was present in 22.1% of the study cohort.
- Presence of angiographically apparent MB was independently associated with the increased risk of life-threatening ventricular arrhythmia in patients with implantable cardioverter defibrillator for primary or secondary prevention of sudden cardiac death.

What Are the Clinical Implications?

- The precise assessment and diagnosis of MB may enhance identification of high-risk patients who could be susceptible to adverse arrhythmic events and benefit from closer follow-up and targeted therapies.
- Despite the relatively benign clinical presentation, patients with angiographically apparent MB had significantly higher risk of life-threatening ventricular arrhythmia compared with those without MB, which may in part account for the underlying mechanisms for poor prognosis in patients with myocardial infarction/ischemia with nonobstructive coronary arteries and offer an important scientific implication for better understanding and management of this condition.

Nonstandard Abbreviations and Acronyms

CAG	coronary angiography
ICM	ischemic cardiomyopathy
LTVA	life-threatening ventricular arrhythmia
MB	myocardial bridge
MINOCA	myocardial infarction/ischemia with nonobstructive coronary arteries
SCD	sudden cardiac death
VSA	vasospastic angina

ventricular arrhythmia,^{17,18} and even sudden cardiac death (SCD).^{5,19,20} These findings have prompted further research interest on the associations between MB and cardiovascular abnormalities. However, it remains unknown whether presence of MB contributes to the increased risk of life-threatening ventricular arrhythmia (LTVA), especially in patients treated with implantable cardioverter defibrillator (ICD) for primary or secondary prevention of SCD who are at the highest risk for LTVA.

Because LTVA and its most common consequence (ie, SCD) constitute major public health concerns, accounting for ≈50% of all cardiovascular deaths, with at least 25% being first symptomatic cardiac events,²¹ the identification of such association is scientifically noteworthy. Therefore, the aim of this study was to explore the possible impact of MB on long-term clinical outcomes in patients with ICD treatment, focusing especially on lethal ventricular arrhythmia.

METHODS

The authors declare that all supporting data are available within the article.

Study Design and Population

This single-center, retrospective, observational study enrolled patients who underwent ICD implantation for primary or secondary prevention of SCD at Yokohama City University Medical Center between January 2001 and January 2017. Because presence of MB was identified by coronary angiography (CAG) in the present study, patients who did not have analyzable CAG images were excluded. Additionally, to isolate the true impact of MB on ventricular arrhythmias as much as possible, patients with cardiac resynchronization therapy, who likely have severely impaired LV dysfunction and the resultant ventricular arrhythmias, were also excluded. All patients received standard medical therapy depending on their underlying heart diseases. Patients were followed for the primary end point that was the first episode(s) of LTVA defined as appropriate ICD treatments (antitachyarrhythmia pacing and/or shock for ventricular tachycardia and/or ventricular fibrillation) or SCD.²² The experienced electrophysiologist analyzed the stored ECG data and categorized LTVA as ventricular tachycardia or ventricular fibrillation based on the rate and morphologic characteristics of each arrhythmic event as well as types of device therapy that terminated ventricular tachyarrhythmias.

The ICD systems used in the present study were manufactured by Medtronic (Minneapolis, MN), Boston Scientific (Marlborough, MA), Abbott Vascular (Mountain View, CA), BIOTRONIK (Berlin, Germany), and Ela Medical (Montrouge, France). In all devices, the stability and sudden onset algorithms were set to reduce inappropriate shocks. The tachycardia detection zones were programmed to recognize fibrillation and either 1 or 2 ventricular tachycardia zones.

The study protocol was approved by the institutional review board at Yokohama City University Medical Center. The institutional review board also gave approval for an opt-out consent method and informed consent was waived because of the retrospective nature of the present study.

Myocardial Bridge

MB was evaluated by CAG, and to clearly establish presence of MB, 2 angiographic views were obtained after intracoronary administration of isosorbide dinitrate because systolic narrowing can be accentuated by intracoronary isosorbide dinitrate injection by vasodilating adjacent nonbridged coronary segments.^{2,3} Angiographically apparent MB was defined as systolic milking appearance with significant arterial compression, defined as $\{[\text{minimum lumen diameter at diastole} - \text{minimum lumen diameter at systole}] / \text{minimum lumen diameter at diastole} \times 100, \%\} \geq 20\%$ by quantitative coronary angiography (Figure 1). In addition to arterial compression, the length of MB was also measured by quantitative coronary angiography in patients with MB. Quantitative coronary angiography analysis was performed using Cardiovascular Angiographic Analysis System (CAAS 5.9, Pie Medical Imaging, Maastricht, Netherlands) at Yokohama City University Medical Center, blinded to clinical information.

Statistical Analysis

Statistical analyses were performed with JMP Pro[®] 12 (SAS Institute Inc., Cary, NC). Data are expressed as frequencies and percentages for categorical variables and as mean \pm SD for continuous variables. Categorical comparisons were performed using a chi-square test or Fisher exact test. Continuous values were compared by using the unpaired Student *t* test, or Wilcoxon rank-sum test, as appropriate. Survival analysis was performed applying by the Kaplan–Meier method and the log-rank test. Hazard ratio and 95% CI were analyzed with the Cox proportional hazards regression models to identify factors associated with LTVA. The proportional hazards assumption was evaluated by complementary log-log plot for each variable before applying the Cox proportional hazards regression model. A $P < 0.05$ was considered statistically significant.

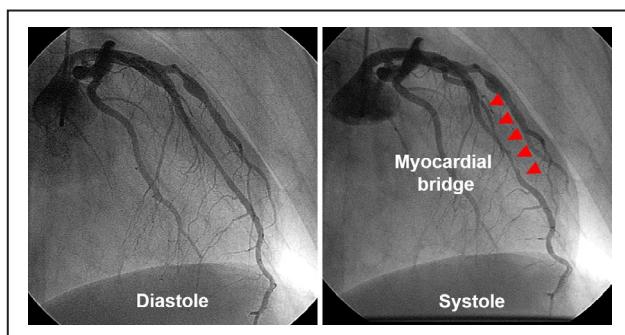


Figure 1. Representative case of myocardial bridge. Left: coronary angiography (CAG) at diastole; Right: CAG at systole. There is a significant arterial compression in the mid of left anterior descending artery.

RESULTS

Baseline Characteristics and Clinical Outcomes

The present study screened 165 consecutive patients who received ICD implantation; among these, 25 patients were excluded because of missing or no CAG images (18 patients underwent CAG at the other hospitals; 7 patients, with no significant findings suggesting myocardial ischemia, did not perform CAG because of their age—too young or old). As a result, a total of 140 patients with ICD treatment for primary ($n=23$) or secondary ($n=117$) prevention were included in this analysis. After ICD implantation, patients were followed for up to 17.8 years (median [interquartile range]: 4.5 [2.2–7.1] years). During this period, LTVA occurred in 53 (37.9%) patients (46 appropriate ICD treatments for ventricular tachycardia and fibrillation, and 7 SCD).

CAG identified MB in 31 (22.1%) patients. Quantitative characteristics of MB by quantitative coronary angiography revealed that MB length was 35.6 ± 12.1 mm and arterial compression was $39.7 \pm 19.6\%$.

Baseline characteristics, medications at the ICD implantation and the indication of ICD implantation (primary or secondary prevention) were similar between patients with and without LTVA, except for lower LV ejection fraction (LVEF) and more frequent involvement of angiographically apparent MB in patients with LTVA than those without LTVA (Table 1).

Factors Associated With Life-Threatening Ventricular Arrhythmia

On univariate analyses, lower LVEF, presence of angiographically apparent MB, lower rates of cardiac channelopathies and higher rates of primary prevention were or tended to be associated with LTVA (Table 2). In multivariate analysis including all variables with a $P \leq 0.10$ on univariate analysis, lower LVEF and presence of angiographically apparent MB were independently associated with higher risk of LTVA (Table 2). Similar results were also observed in a sensitive analysis restricted to patients with ICD treatment for primary prevention (hazard ratio, 14.53; 95% CI, 1.48–142.31; $P=0.02$) or secondary prevention, or patients with ischemic heart disease (ischemic cardiomyopathy [ICM] and VSA) (Tables 3 and 4).

Life-Threatening Ventricular Arrhythmia in Patients With Versus Without Myocardial Bridge

Patients with angiographically apparent MB showed younger age, higher prevalence of VSA, lower rates of ICM, coronary risk factors (hypertension, dyslipidemia, and diabetes mellitus), prior myocardial

Table 1. Baseline Characteristics

Variables	All (n=140)	LTVAE (n=53)	Non-LTVAE (n=87)	P Value
Age, y	60±14	58±14	61±14	0.16
Male, n (%)	117 (83.6)	47 (88.7)	70 (80.5)	0.19
Ischemic cardiomyopathy, n (%)	56 (40.0)	23 (43.4)	33 (37.9)	0.52
Vasospastic angina, n (%)	31 (22.1)	14 (26.4)	17 (19.5)	0.35
NICM*, n (%)	42 (30.0)	13 (24.5)	29 (33.3)	0.27
Cardiac channelopathies†, n (%)	11 (7.9)	3 (5.7)	8 (9.2)	0.53
Current or former smoker, n (%)	97 (69.8)	35/52 (67.3)	62 (71.3)	0.62
Hypertension, n (%)	83 (59.3)	29 (54.7)	54 (62.1)	0.39
Dyslipidemia, n (%)	93 (66.4)	36 (67.9)	57 (65.5)	0.77
Diabetes mellitus, n (%)	41 (29.3)	12 (22.6)	29 (33.3)	0.17
Family history of premature CAD, n (%)	7 (5.0)	3 (5.7)	4 (4.6)	1.00
Prior myocardial infarction, n (%)	47 (33.6)	21 (39.6)	26 (29.9)	0.24
Prior percutaneous coronary intervention, n (%)	39 (27.9)	17 (32.1)	22 (25.3)	0.39
Prior CABG, n (%)	13 (9.3)	7 (13.2)	6 (6.9)	0.24
Medication at ICD treatment				
Aspirin, n (%)	69 (49.3)	28 (52.8)	41 (47.1)	0.51
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, n (%)	72 (51.4)	29 (54.7)	43 (49.4)	0.54
Statin, n (%)	81 (57.9)	30 (56.6)	51 (58.6)	0.81
Calcium channel blocker, n (%)	59 (42.1)	24 (45.3)	35 (40.2)	0.56
Beta blocker, n (%)	90 (64.3)	33 (62.3)	57 (65.5)	0.70
Isosorbide dinitrate, n (%)	31 (22.1)	12 (22.6)	19 (21.8)	0.91
Nicorandil, n (%)	46 (33.1)	15 (28.3)	31 (36.0)	0.34
Antidiabetic drugs, n (%)	20 (14.3)	6 (11.3)	14 (16.1)	0.43
Insulin, n (%)	4 (2.9)	2 (3.8)	2 (2.3)	0.63
Diuretics, n (%)	57 (40.7)	19 (35.8)	38 (43.7)	0.36
Pimobendane, n (%)	10 (7.1)	5 (9.4)	5 (5.7)	0.50
Anti-arrhythmia drugs‡, n (%)	52 (37.1)	23 (43.4)	29 (33.3)	0.23
ICD indication				0.29
Primary prevention, n (%)	23 (16.4)	11 (20.8)	12 (13.8)	
Secondary prevention, n (%)	117 (83.6)	42 (79.2)	75 (86.2)	
LVEF, %	52.9±17.3	49.2±15.0	55.3±18.2	0.02
Left ventricular end-diastolic diameter, mm	54.1±8.9	54.5±8.2	53.9±9.3	0.54
LVEF ≤35%	25 (17.9)	11 (20.8)	14 (16.1)	0.49
Myocardial bridge, n (%)	31 (22.1)	24 (45.3)	7 (8.0)	<0.0001

Values are number (%) or mean±SD. *P* values for LTVAE vs non-LTVAE. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; ICD, implantable defibrillator; LTVAE, life-threatening ventricular arrhythmic events; LVEF, left ventricular ejection function; and NICM, nonischemic cardiomyopathy.

NICM include dilated cardiomyopathy, hypertrophic cardiomyopathy, cardiac sarcoidosis, myocarditis, alcoholic cardiomyopathy, amyloidosis, drug-induced cardiomyopathy, congenital heart disease, valvular heart disease, left ventricular noncompaction cardiomyopathy, and cardiomyopathy with unknown reasons.*

Cardiac channelopathies include congenital long QT syndrome, Brugada syndrome, and idiopathic ventricular tachycardia/fibrillation.†

Anti-arrhythmia drugs include amiodarone, bepridil, sotalol, mexiletine, and/or verapamil. Categorical comparisons were performed using Fisher's exact test for cardiac channelopathies, family history of premature CAD, prior CABG, insulin and pimobendane, and chi-square test for the other variables. Continuous values were compared using Wilcoxon rank-sum test.‡

infarction (MI), prior percutaneous coronary intervention and treatment drugs for coronary artery disease (CAD) and/or heart failure (ie, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, statin, beta blocker, antidiabetic drugs, diuretics), and more preserved LVEF, compared with those without (Table 5).

Despite the relatively benign clinical presentation in patients with angiographically apparent MB as mentioned earlier, LTVA was more frequently observed in patients with angiographically apparent MB compared with those without (77.4% versus 26.6%, $P<0.0001$). Kaplan–Meier analysis over a median (interquartile range) follow-up period of 4.5 (2.2–7.1)

Table 2. Factors Associated With Life-Threatening Ventricular Arrhythmia

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Age, per 1 y	0.997	0.98–1.02	0.72			
Male	2.03	0.86–4.79	0.11			
Ischemic cardiomyopathy	1.29	0.75–2.22	0.36			
Vasospastic angina	1.66	0.89–3.08	0.11			
Nonischemic cardiomyopathy	0.72	0.39–1.34	0.31			
Cardiac channelopathies	0.36	0.11–1.18	0.09	0.40	0.11–1.39	0.15
Current or former smoker	0.85	0.48–1.52	0.59			
Hypertension	0.89	0.52–1.54	0.68			
Dyslipidemia	1.13	0.63–2.01	0.68			
Diabetes mellitus	0.82	0.43–1.57	0.55			
Prior myocardial infarction	1.34	0.77–2.32	0.30			
Aspirin	1.31	0.76–2.24	0.33			
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1.40	0.81–2.43	0.23			
Statin	0.96	0.56–1.66	0.89			
Calcium channel blocker	1.24	0.72–2.13	0.44			
Beta blocker	0.95	0.54–1.65	0.84			
Isosorbide dinitrate	0.98	0.52–1.87	0.96			
Nicorandil	0.92	0.51–1.68	0.80			
Diuretics	0.88	0.50–1.54	0.65			
Pimobendane	1.95	0.77–4.92	0.16			
Anti-arrhythmia drugs	1.49	0.86–2.57	0.15			
ICD for primary prevention	1.76	0.90–3.42	0.10	1.12	0.56–2.23	0.74
LVEF, per –1%	1.02	1.00–1.04	0.003	1.03	1.01–1.05	0.0008
Left ventricular end-diastolic diameter, per 1 mm	1.02	0.99–1.05	0.21			
LVEF ≤35%	1.98	1.01–3.89	0.046			
Myocardial bridge	3.02	1.76–5.19	<0.0001	4.24	2.39–7.55	<0.0001

All variables with a $P \leq 0.10$ were included in multivariate analysis. With respect to LVEF, only LVEF (per –1%) was included in the multivariate analysis because of its lower P value than that of LVEF $\leq 35\%$. HR indicates hazard ratio; ICD, implantable defibrillator; and LVEF, left ventricular ejection function.

years revealed a significantly lower event-free rate in patients with angiographically apparent MB compared with those without ($P < 0.0001$ for log-rank) (Figure 2). This finding persisted when the analysis was limited to patients with ICD treatment for primary prevention (100% versus 25.0%, $P = 0.04$ for log-rank) or secondary prevention (70.8% versus 26.9%, $P = 0.001$ for log-rank), or patients with ischemic heart disease (ICM and VSA) (72.2% versus 34.8%, $P = 0.009$ for log-rank). Of note, among patients with ICD treatment for primary prevention, all patients with angiographically apparent MB experienced LTVA, indicating the potential impact of angiographically apparent MB on the occurrence of LTVA.

The association between angiographically apparent MB and LTVA was also preserved in multivariate analyses adjusting for several clinical differences between

patients with and without angiographically apparent MB: Model 1 adjusted for ICM (obstructive CAD), VSA, prior MI, prior PCI, and LVEF; Model 2 adjusted for age, hypertension, dyslipidemia, and diabetes mellitus; and Model 3 adjusted for medical treatments (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statin, beta blocker, antidiabetic drugs, diuretics) (Table 6).

Although sufficient analyses regarding characteristics of MB could not be performed because of small sample size, MB length tended to be longer in patients with versus without LTVA (37.7 ± 13.0 mm versus 28.8 ± 3.8 mm, $P = 0.09$), whereas arterial compression did not differ between both groups of patients ($39.8 \pm 20.6\%$ versus $39.1 \pm 17.5\%$, $P = 1.00$) primarily attributable to the selection bias (only MB patients with angiographically significant arterial compression were evaluated in this study).

Table 3. Factors Associated With Life-Threatening Ventricular Arrhythmia in Patients With ICD for Secondary Prevention (n=117)

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Age, per 1 y	0.995	0.98–1.02	0.64			
Male	1.64	0.69–3.93	0.27			
Ischemic cardiomyopathy	1.22	0.66–2.24	0.53			
Vasospastic angina	1.97	1.02–3.80	0.04	4.18	1.69–10.36	0.002
Nonischemic cardiomyopathy	0.56	0.23–1.33	0.19			
Cardiac channelopathies	0.38	0.11–1.27	0.12			
Current or former smoker	0.69	0.37–1.32	0.26			
Hypertension	0.72	0.39–1.32	0.29			
Dyslipidemia	1.16	0.60–2.24	0.66			
Diabetes mellitus	0.80	0.38–1.68	0.56			
Prior myocardial infarction	1.23	0.66–2.29	0.51			
Aspirin	1.67	0.90–3.09	0.10	1.52	0.81–2.82	0.19
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1.27	0.68–2.35	0.45			
Statin	1.20	0.64–2.26	0.57			
Calcium channel blocker	1.32	0.72–2.45	0.37			
Beta blocker	0.73	0.40–1.36	0.32			
Isosorbide dinitrate	0.96	0.47–1.95	0.91			
Nicorandil	0.91	0.47–1.76	0.78			
Antidiabetic drugs	0.78	0.31–1.98	0.60			
Diuretics	0.68	0.36–1.32	0.26			
Pimobendane	1.03	0.25–4.28	0.97			
Anti-arrhythmia drugs	1.17	0.62–2.18	0.63			
LVEF, per –1%	1.02	1.00–1.04	0.01	1.05	1.03–1.08	<0.0001
Left ventricular end-diastolic diameter, per 1 mm	1.02	0.9–1.06	0.19			
LVEF ≤35%	1.98	0.91–4.30	0.09			
Myocardial bridge	2.71	1.46–5.03	0.002	3.17	1.62–6.20	0.0008

All variables with a $P \leq 0.10$ were included in multivariate analysis. With respect to LVEF, only LVEF (per –1%) was included in the multivariate analysis because of its lower P value than that of LVEF $\leq 35\%$. HR indicates hazard ratio; ICD, implantable defibrillator; and LVEF, left ventricular ejection function.

DISCUSSION

The main findings of this study are as follows: (1) among patients treated with ICD for primary or secondary prevention of SCD, 37.9% of the patients subsequently experienced LTVA (appropriate ICD treatments for ventricular tachycardia and/or ventricular fibrillation, or sudden cardiac death), whereas angiographically apparent MB was present in 22.1% of the patients; and (2) in addition to LV dysfunction, presence of angiographically apparent MB was independently associated with the increased risk of LTVA in the multivariate analysis. To the best of our knowledge, this is the first study to reveal the prevalence of MB by CAG in patients with ICD treatment and to potentially indicate angiographically apparent MB as an important risk factor for long-term arrhythmic events in this population.

Prevalence of Myocardial Bridge in Patients With ICD

The prevalence of MB remains undefined and the reported incidence of MB varies widely according to the population studied and the methods of evaluation: 0.5% to 16% in resting conditions up to 40% with intracoronary injection of nitroglycerine and/or provocative tests using acetylcholine or dobutamine by CAG,^{4,9} 3.5% to 58% by coronary computed tomography angiography (CCTA),²³ 23% to 58% by intravascular ultrasound (IVUS),^{24,25} and 5% to 86% in autopsy series.²⁶ Saito et al⁹ used CAG to report that MB was present in 36% of the patients without coronary stent in the LAD who underwent acetylcholine provocative test. Tsujita et al²⁴ reported the incidence of MB as 23% by IVUS in patients with de novo coronary lesions in the LAD. The present study focused for the first time

Table 4. Factors Associated With Life-Threatening Ventricular Arrhythmia in Patients With Ischemic Heart Disease (ICM and VSA) (n=87)

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
Age, per 1 y	0.98	0.96–1.01	0.21			
Male	1.25	0.38–4.09	0.71			
Current or former smoker	0.67	0.32–1.39	0.28			
Hypertension	0.45	0.23–0.86	0.02	0.66	0.32–1.33	0.24
Dyslipidemia	0.82	0.39–1.74	0.60			
Diabetes mellitus	0.90	0.45–1.79	0.76			
Prior myocardial infarction	1.19	0.62–2.28	0.59			
Aspirin	1.15	0.58–2.30	0.69			
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1.18	0.62–2.25	0.62			
Statin	0.82	0.40–1.69	0.59			
Calcium channel blocker	1.23	0.64–2.35	0.54			
Beta blocker	0.71	0.37–1.36	0.30			
Isosorbide dinitrate	0.81	0.40–1.64	0.55			
Nicorandil	0.57	0.29–1.12	0.10	0.68	0.34–1.35	0.27
Antidiabetic drugs	0.80	0.34–1.93	0.63			
Diuretics	0.67	0.33–1.36	0.27			
Pimobendane	1.73	0.53–5.64	0.37			
Anti-arrhythmia drugs	1.51	0.78–2.91	0.22			
LVEF, per –1%	1.03	0.94–1.07	0.10	1.03	1.01–1.05	0.01
Left ventricular end-diastolic diameter, per 1 mm	1.02	0.98–1.06	0.44			
LVEF ≤35%	1.89	0.86–4.14	0.11			
Myocardial bridge	2.41	1.23–4.76	0.01	3.05	1.37–6.79	0.006

All variables with a $P \leq 0.10$ were included in multivariate analysis. CCB indicates calcium channel blocker; HR, hazard ratio; ICM, ischemic cardiomyopathy; LVEF, left ventricular ejection function; and VSA, vasospastic angina.

on patients with ICD treatment for primary or secondary prevention of SCD who had various cardiac conditions (ICM, VSA, nonischemic cardiomyopathy, cardiac channelopathies, etc), and identified MB in 22.1% of the patients by CAG, being in line with previous studies and contributing to the growing body of evidence of the prevalence of MB. Although CAG remains the most common technique for diagnosing MB, it can also underdiagnose MB especially in patients with weak systolic arterial compression because the diagnosis of MB by CAG is usually made only indirectly by detecting the characteristic “milking” effect, rather than by directly visualizing the structure of MB. Therefore, future studies using CCTA and IVUS are warranted to address the exact prevalence of MB in this population.

Impact of Myocardial Bridge on Life-Threatening Ventricular Arrhythmia

Previous studies have reported the associations of MB with significant increases in exercise-induced premature ventricular contraction and nonsustained ventricular tachycardia as well as increases in postexercise

QT dispersion and repolarization abnormalities, all of which are well-known predictors for ventricular tachyarrhythmias and cardiovascular mortality.^{17,18} The present study extends these studies and provides further evidence that presence of angiographically apparent MB was also associated with the increased risk of LTVA in patients with ICD treatment. Although the exact mechanism for this association remains to be elucidated, one triggering mechanism for LTVA may be myocardial ischemia caused by MB-induced mechanical compression. Multiple studies support this thought and have repeatedly shown that hemodynamically significant MB can predispose to myocardial ischemia due to both functional and anatomical abnormalities, including reduced coronary blood perfusion due to limited diastolic filling time by arterial compression that can be worsened by exercise and tachycardia,^{5,8} impaired coronary flow reserve,¹ endothelial dysfunction and vasospasm both at rest and during exercise,^{9–12} systolic and diastolic LV dysfunction and stunning,^{15,16} and accelerated proximal plaque formation.^{7,13} Irrespective of the presence of MB, these cardiac abnormalities have been associated with incident and recurrent LTVA in

Table 5. Baseline Characteristics: Patients With Versus Without MB

Variables	MB (n=31)	Non-MB (n=109)	P Value
Age, y	54±15	62±13	0.01
Male, n (%)	26 (83.9)	91 (83.5)	0.96
Ischemic cardiomyopathy, n (%)	5 (16.1)	51 (46.8)	0.001
Vasospastic angina, n (%)	13 (41.9)	18 (16.5)	0.004
Nonischemic cardiomyopathy, n (%)	9 (29.0)	33 (30.3)	0.89
Cardiac channelopathies, n (%)	4 (12.9)	7 (6.4)	0.26
Current or former smoker, n (%)	22 (71.0)	75/108 (64)	0.87
Hypertension, n (%)	14 (45.2)	69 (63.3)	0.07
Dyslipidemia, n (%)	16 (51.6)	77 (70.6)	0.05
Diabetes mellitus, n (%)	3 (9.7)	38 (34.9)	0.003
Family history of premature CAD, n (%)	2 (6.5)	5 (4.6)	0.65
Prior myocardial infarction, n (%)	5 (16.1)	42 (38.5)	0.01
Prior percutaneous coronary intervention, n (%)	4 (12.9)	35 (32.1)	0.03
Prior CABG, n (%)	1 (3.2)	12 (11.0)	0.30
Medication			
Aspirin, n (%)	13 (41.9)	56 (51.4)	0.35
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, n (%)	11 (35.5)	61 (56.0)	0.04
Statin, n (%)	12 (38.7)	69 (63.3)	0.01
Calcium channel blocker, n (%)	17 (54.8)	42 (38.5)	0.11
Beta blocker, n (%)	15 (48.4)	75 (68.8)	0.04
Isosorbide dinitrate, n (%)	10 (32.3)	21 (19.3)	0.14
Nicorandil, n (%)	7 (22.6)	39 (36.1)	0.15
Antidiabetic drugs, n (%)	1 (3.2)	19 (17.4)	0.08
Insulin, n (%)	0 (0)	4 (3.7)	0.58
Anti-arrhythmia drugs*	10 (32.3)	42 (38.5)	0.52
Diuretics, n (%)	6 (19.4)	51 (46.8)	0.004
Pimobendane, n (%)	2 (6.5)	8 (7.3)	1.00
Implantable defibrillator indication			0.31
Primary prevention, n (%)	7 (22.6)	16 (14.7)	
Secondary prevention, n (%)	24 (77.4)	93 (85.3)	
LVEF (%)	60.1±15.1	50.9±17.4	0.009
Left ventricular end-diastolic diameter, mm	49.9±7.6	55.4±8.8	0.002
LVEF ≤35%	2 (6.5)	23 (21.1)	0.04

Values are number (%) or mean±SD. *P* values for MB vs non-MB. Categorical comparisons were performed using Fisher's exact test for cardiac channelopathies, family history of premature CAD, prior CABG, antidiabetic drugs, insulin and pimobendane, and chi-square test for the other variables. Continuous values were compared using Wilcoxon rank-sum test. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection function; and MB, myocardial bridge.

patients with ICD treatment.²⁷⁻²⁹ A past comprehensive imaging study using CAG with IVUS, dobutamine stress diastolic fractional flow reserve, and CCTA also demonstrated that the length of MB (longer MB length) as well as angiographically apparent MB had a reasonable likelihood to be hemodynamically relevant MB defined as diastolic fractional flow reserve ≤0.76 in patients with recurrent symptoms of typical angina without obstructive CAD,³⁰ which results may partially explain our results of a tendency toward longer MB length seen in patients with versus without LTVA among patients with angiographically apparent MB and indirectly support possible association between

MB-induced ischemia and LTVA. On the other hand, previous autopsy series of subjects with SCD have reported that hemodynamically significant MB relates to increased myocardial fibrosis and interstitial edema in the MB area, both of which can increase the risk of electrical instability,^{5,19,20} and the relationships may represent additional mechanisms contributing to adverse arrhythmic events in patients with MB. In summary, these findings from previous studies and the current study suggest that MB itself may potentially be an important risk factor for the development of LTVA.

The severity of myocardial ischemia by MB depends on several factors, including the length, depth, and

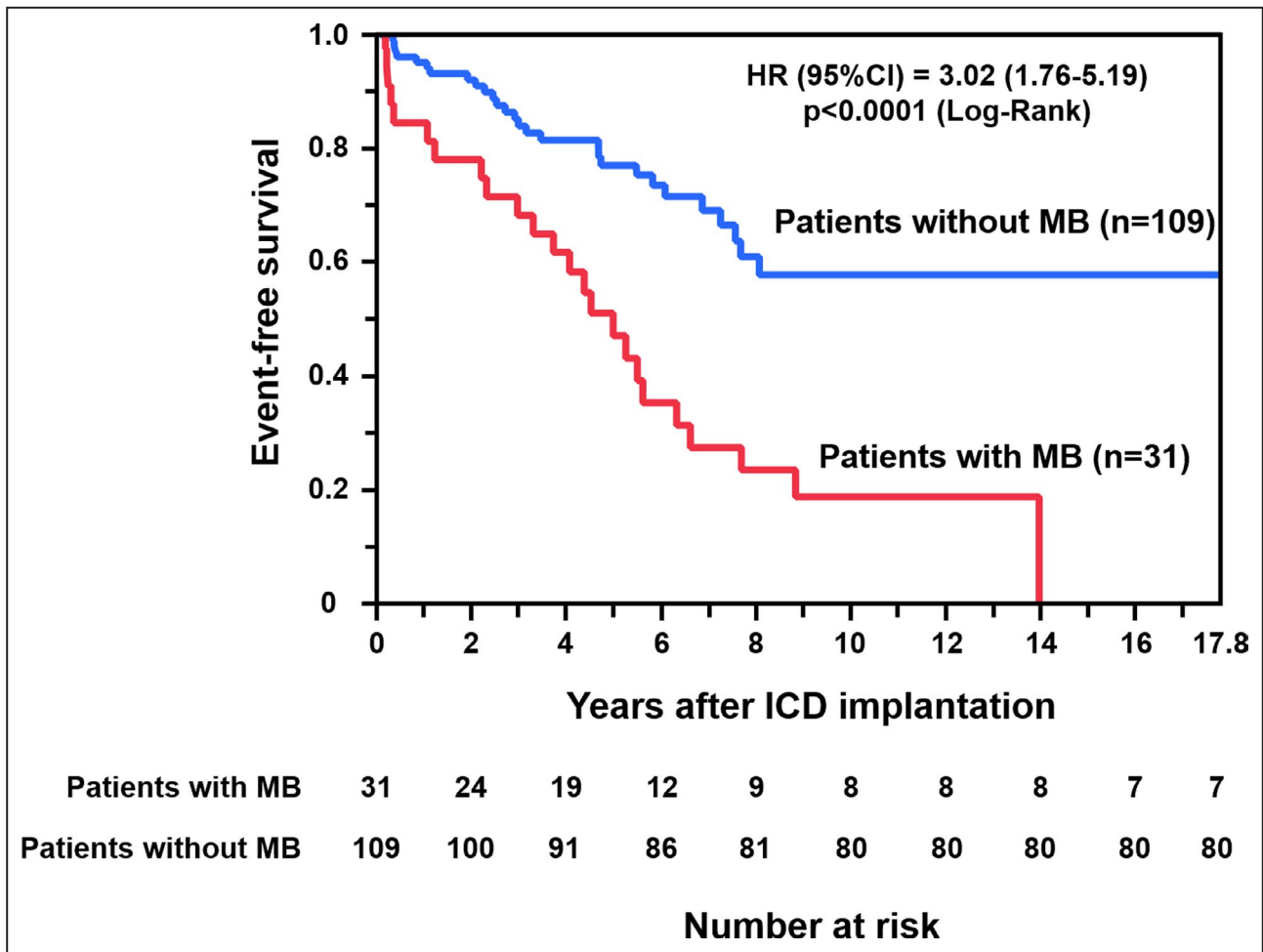


Figure 2. Life-threatening ventricular arrhythmia: patients with vs without myocardial bridge. Kaplan–Meier analysis over a median (interquartile range) follow-up period of 4.5 (2.2–7.1) years demonstrated a significantly lower event-free rate in patients with vs without angiographically apparent MB among patients who underwent ICD implantation for primary or secondary prevention of SCD. HR indicates hazard ratio; ICD, implantable defibrillator; MB, myocardial bridge; and SCD, sudden cardiac death.

thickness of the MB, as well as the degree of arterial compression.^{6,7,13,30} The present study was unable to address the impact of these MB parameters on LTVA because of the limited capability of CAG as mentioned earlier. Therefore, the detailed and direct assessment of MB using more advanced imaging modalities (ie, CCTA and IVUS) may offer additional insights into the results of the current study.

Clinical Implication and Future Perspective

One clinically important finding of the current study is that despite its relatively benign clinical presentation (ie, younger age, lower rates of coronary risk factors and CAD, and greater LVEF), patients with MB had significantly higher rates of LTVA compared with those without MB, which may in part account for the underlying mechanisms for poor prognosis in

patients with MI/ischemia with nonobstructive coronary arteries (MINOCA). MINOCA is a heterogeneous syndrome with different etiologies, whereas MB does not appear to be a rare finding and cause of MINOCA. Indeed, Lee et al²⁵ comprehensively evaluated multiple different mechanisms in a prospective cohort with symptoms suggesting CAD without apparent flow-limiting obstruction on CAG (ie, MINOCA) and revealed that MB was present in 58% of the patients by IVUS, which is much higher than that in a previous IVUS report of patients with CAD.²⁴ They also found that almost two thirds of MB patients had other coexisting coronary abnormalities such as coronary endothelial dysfunction and VSA, occult epicardial coronary atherosclerosis, and microvascular dysfunction, all of which are associated with MB as mentioned earlier, possibly indicating that MB may play a contributory role in the occurrence and development of MINOCA. Additionally, similar to the

Table 6. Impact of MB on LTVA: Multivariate Analyses Adjusting for Several Clinical Differences Between Patients With and Without Angiographically Apparent MB

Variable	Model 1			Model 2			Model 3				
	HR	95% CI	P Value	Variable	HR	95% CI	P Value	Variable	HR	95% CI	P Value
ICM	1.17	0.46–2.98	0.74	Age	0.99	0.97–1.01	0.28	ACEI/ARB	2.06	1.05–4.04	0.04
VSA	3.48	1.05–11.55	0.04	Hypertension	1.23	0.67–2.28	0.50	Statin	1.29	0.72–2.32	0.39
Prior MI	1.65	0.59–4.58	0.34	Dyslipidemia	1.47	0.79–2.74	0.22	Beta blocker	0.99	0.50–1.96	0.99
Prior PCI	1.04	0.49–2.19	0.34	Diabetes mellitus	1.04	0.52–2.07	0.91	Antidiabetic drugs	0.91	0.37–2.24	0.84
LVEF	1.05	1.03–1.07	<0.0001	MB	3.25	1.82–5.82	<0.0001	Diuretics	0.89	0.44–1.80	0.75
MB	4.51	2.42–8.40	<0.0001					MB	3.75	2.01–7.00	<0.0001

Table 6 represents multivariate analyses adjusting for several clinical differences between patients with and without angiographically apparent MB: Model 1 adjusted for ICM (obstructive coronary artery disease), VSA, prior MI, prior PCI and LVEF; Model 2 adjusted for age, hypertension, dyslipidemia, and diabetes mellitus; and Model 3 adjusted for medical treatments drugs (ACEI/ARB, statin, beta blocker, antidiabetic drugs, diuretics), respectively. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; ICM, ischemic cardiomyopathy; LTVA, life-threatening ventricular arrhythmia; LVEF, left ventricular ejection fraction; MB, myocardial bridge; MI, myocardial infarction; PCI, percutaneous coronary intervention; and VSA, vasospastic angina.

results of the current study, patients with MINOCA have been reported to have lower risk profiles than their counterparts with MI by obstructive CAD; nevertheless, the reported mortality rates of MINOCA are comparable to those of MI by obstructive CAD,^{31,32} and some deaths are presumed to be owing to lethal ventricular arrhythmias possibly related to MB. Although further studies will need to verify this hypothesis by systematically investigating the causes of death and their relationships with MB in patients with MINOCA, the present study may offer an important scientific implication in better understanding and management of MINOCA.

Contrary to the improved understanding of this unique pathology (ie, MB), treatment options for patients with MB remain limited because there have been no randomized clinical trials addressing what therapies should be recommended to improve long-term clinical outcomes in patients with MB. In general, first-line therapy of symptomatic MB patients is medical treatments with beta blockers, non-dihydropyridine calcium-channel blockers, and/or nitrates.^{1,2,4} Surgical myotomy (or unroofing), intracoronary stenting, and coronary artery bypass graft surgery may also be alternative treatment options, especially for patients with MB who are refractory to maximal medical treatments. Although the present study observed several differences in medications between patients with and without angiographically apparent MB, which was primarily attributable to the differences in their underlying cardiac diseases, further investigation is required to determine the possible protective effects of these therapies against the development of LTVA in patients with MB.

Study Limitations

The present study has several limitations. First, this was a retrospective, single-center analysis with a relatively small sample size and the study cohort was heterogeneous. The present study also included only patients with MB who had significant arterial compression on CAG (ie, angiographically apparent MB) and a consistent number of patients were excluded because of missing or no CAG images, which may limit generalization of the present findings to overall MB. Therefore, our findings need to be confirmed in prospective trials with predefined end points in a larger population with various cardiac conditions and MB types. Second, the present study observed clear unbalance in clinically relevant factors such as impaired LV dysfunction and medical treatment drugs (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statin, and beta blocker, etc) between patients with and without angiographically apparent MB. Although a significant association

between angiographically apparent MB and LTVA was observed in multivariate analyses adjusting for these clinical differences, the observation might theoretically have influenced the results not in favor of angiographically apparent MB. Third, because the direct evidence of the hemodynamic significance and symptoms of MB was not established in the present study, the underlying mechanisms of the association between MB and LTVA remain a matter of speculation. Fourth, the association of the MB severity with detailed characteristics of arrhythmic events (eg, arrhythmic events during exercise or rest, etc) remains unknown. Fifth, because of the limited capability of ICD to identify the origin of LTVA, it is also unknown whether the MB-related LTVA originated in the right ventricular outflow tract or the LV septal wall, areas likely affected by MB. Addressing this clinically important question may offer some clues regarding the impact of MB on LTVA. Sixth, MB predominantly involves the LAD, whereas some autopsy series find right coronary artery and left circumflex artery involvements at similar rates.⁴ Although it is much less likely that MB in the right coronary artery and left circumflex artery has the same impact as MB in the LAD because the branches originating from the right coronary artery and left circumflex artery are penetrating the muscle for a much shorter distance and much less likely to be underperfused, it is unclear whether MB in the right coronary artery and/or left circumflex artery could offer additional prognostic values. Finally, as discussed earlier, the present study was conducted using CAG with limited capability of identifying MB and its severity and was not designed to further stratify patients with MB using anatomical and/or functional CCTA/IVUS findings with sufficient statistical power, which warrants future investigations.

CONCLUSIONS

Presence of angiographically apparent MB was independently associated with life-threatening ventricular arrhythmia in patients with ICD treatment for primary or secondary prevention of SCD. The present study suggests that the precise assessment and diagnosis of MB may enhance identification of high-risk patients who could be susceptible to adverse arrhythmic events and benefit from closer follow-up and targeted therapies.

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Affiliations

From the Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan (K.O., K.H., Y.O., N.M., S.K., H.K., J.K., R.S., H.N., Y.M.,

Y.K., E.A., Y.M., N.I., M.K., T.E., K.T., K.K.); and Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan (K.T.).

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