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ABOUT COVER

Editorial Board Member of *World Journal of Cardiology*, Hiroki Teragawa, MD, PhD, Head of Department, Department of Cardiovascular Medicine, JR Hiroshima Hospital, 3-1-36 Futabanosato, Higashi-Ku, Hiroshima 732-0057, Japan. hiroki-teragawa@jrhh.or.jp

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

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ORIGINAL ARTICLE

Retrospective Study

Does the intracoronary pressure differ according to two types (diffuse or focal) of coronary spasm?

Hiroki Teragawa, Chikage Oshita, Yuko Uchimura

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Hiroki Teragawa, Chikage Oshita, Yuko Uchimura, Department of Cardiovascular Medicine, JR Hiroshima Hospital, Hiroshima 732-0057, Japan

Corresponding author: Hiroki Teragawa, FACC, FACP, FAHA, FESC, MD, PhD, Chief Physician, Doctor, Department of Cardiovascular Medicine, JR Hiroshima Hospital, 3-1-36 Futabanosato, Higashi-Ku, Hiroshima, 732-0057, Japan. hiroki-teragawa@jrhh.or.jp

Abstract

BACKGROUND

Several reports show that two types of coronary vasospasm (diffuse and focal spasm) are associated with the severity or prognosis of coronary spasm in patients with vasospastic angina (VSA). It is unclear whether intracoronary pressure differs between the two spasm types.

AIM

To investigate such relationships using a pressure wire during the spasm provocation test (SPT) in patients with VSA.

METHODS

Eighty-seven patients with VSA (average age: 67 years; 50 men, 37 women) underwent SPT. During the SPT, a pressure wire was advanced into the distal portion of the right coronary artery and left anterior descending coronary artery, and the ratio of the intracoronary pressure to the aortic pressure (Pd/Pa) was continuously monitored. An SPT was performed using acetylcholine (ACh), and the presence of coronary spasm was defined as the presence of > 90% arterial narrowing in response to an ACh infusion, with the usual chest symptoms and/or ischemic ECG changes. Focal spasm was defined as total or subtotal spasm within one segment of the AHA classification, while diffuse spasm was defined as > 90% spasm with two or more segments.

RESULTS

Among 87 patients, the frequencies of metabolic syndrome and having coronary atherosclerosis were higher in the focal group (n = 33) than in the diffuse spasm group (n = 54, P < 0.05). In the vessel analyses, in these 134 spastic segments, diffuse and focal spasms were detected in 100 and 34 vessels, respectively. The Pd/Pa at baseline was similar in both groups (diffuse: 0.96 ± 0.05, focal: 0.95 ± 0.05, P = 0.35); however, the Pd/Pa during coronary spasm was lower in focal spastic vessels (0.66 ± 0.20) than in diffuse spastic vessels (0.76 ± 0.11, P < 0.01),

and the reduction in Pd/Pa during an SPT was also lower in focal spastic vessels (-0.29 ± 0.20) than in diffuse spastic vessels (-0.18 ± 0.11, $P < 0.01$). The presence of focal spasm was a significant factor responsible for reduction in Pd/Pa during SPT.

CONCLUSION
These findings suggest that focal spasm may be more severe than diffuse spasm, judging from the intracoronary pressure during coronary spasm.

Key Words: Acetylcholine; Intracoronary pressure; Diffuse or focal spasm; Vasospastic angina

Core Tip: Coronary spasm is classified into diffuse spasm and focal spasm based on its morphology; it is noted that focal spasm may have a worse prognosis. We compared the clinical backgrounds of patients with focal spasms. We also evaluated the intracoronary pressure in diffuse and focal spasms using a pressure wire. Patients in the focal spasm group were more likely to have metabolic syndrome and coronary atherosclerosis. The reduction in intracoronary pressure during coronary spasms was greater in focal spasms than in diffuse spasms. These findings suggest that the degree of ischemia may be greater in patients with focal spasms.

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INTRODUCTION

Coronary spasm is the transient vasoconstriction of epicardial coronary arteries that leads to the occurrence of myocardial ischemia[1] and is considered the cause of not only rest angina and effort angina but also acute coronary syndrome or ischemic cardiac arrest[1,2]. Guidelines and expert consensus documents on coronary spasms and vasospastic angina (VSA) have already been published, and more interest has been focused on coronary spasms since they have been identified as a cause of ischemia with nonobstructive coronary artery disease (INOCA) or myocardial infarction with nonobstructive coronary artery disease (MINOCA)[3].

However, several issues regarding coronary spasm are not fully understood or solved, including the protocol for the spasm provocation test (SPT), the sequence of SPT during comprehensive coronary angiography, the treatment of medically refractory coronary spasm, and the need for implantable cardioverter defibrillators in the event of cardiac arrest[2-6]. The endotype of coronary spasm as focal and diffuse spasm is one such unsolved problem regarding coronary spasm[5]. The clinical characteristics of these two types of coronary spasm have been reported to be different: focal spasm occurs more frequently in men than in women[7,8] and is more frequently recognized in atherosclerotic lesions than diffuse spasm[9]. Regarding prognosis, it has been demonstrated that the prognosis is worse in patients with VSA and focal spasm than in those with diffuse spasm[7,10,11]. The cause of the worse prognosis in focal spasm than in diffuse spasm may, in part, be the progression of atherosclerosis or destabilization of the atherosclerotic lesion with focal spasm[9,12-15]. The severity of myocardial ischemia due to focal or diffuse coronary spasm may be one of the possible mechanisms responsible for the difference in prognosis between the two types of coronary spasm; however, the method of assessing the severity of myocardial ischemia due to focal or diffuse spasm has been unclear.

Intracoronary pressure assessment was originally adopted in the clinical setting to assess the immediate coronary stenosis[16], and the distal pressure (Pd) divided by the aortic pressure (Pa) during hyperemia, which has been recognized as the fractional flow reserve (FFR), decreases according to myocardial ischemia[17]. Intracoronary pressure assessments during SPT have recently been used[18,19]. Furthermore, recently, in European countries and the United States, SPT has been performed after an assessment of coronary microvascular function using a pressure wire or Doppler wire[3], which means that there may be more opportunities to perform SPT using a pressure wire[20]. Thus, in the present study, we clarified the clinical characteristics of patients with VSA who manifested focal spasm during the SPT compared with those of patients with VSA who manifested diffuse spasm during the SPT and investigated whether the severity of myocardial ischemia (shown by the Pd/Pa during SPT) differed according to the type of spasm (focal or diffuse spasm).

MATERIALS AND METHODS

Study patients

This observational retrospective study included patients with VSA diagnosed with SPT using a pressure wire who visited our institution between January 2012 and March 2017 (n = 98). The exclusion criteria were as follows: Significant coronary stenosis (%stenosis > 50%, n = 7) or a previous medical history of percutaneous coronary intervention (n = 4). Ultimately, 87 patients were enrolled in the present study. The study protocol was approved by the ethics committee of our institution. Written informed consent was obtained from all participants.

Coronary angiography and SPT using a pressure wire

SPT was performed as previously described[21]. During this period, SPT were performed on the right coronary artery (RCA) at our institution. After the initial Coronary angiography (CAG), a 0.014-inch pressure wire (PrimeWire Prestige Plus Guide Wire or Verrata Pressure Guide Wire; Phillips Volcano, Amsterdam, Holland) was advanced through a 5-Fr catheter into the distal segments of the RCA. Before this, we calibrated the pressure between the tips of the catheters and the pressure wire at the ostium of the coronary arteries. The ratios of distal intracoronary pressure (Pd), derived from the pressure wire, to Pa, derived from the catheter tips (Pd/Pa index), were continuously monitored. Subsequently, 20 μg and 50 μg doses of acetylcholine (ACh) were injected into the RCA. When coronary spasm was not induced by 50 μg ACh, a maximum dose of 80 μg ACh was infused into the RCA. The minimal Pd/Pa index in response to each ACh dose was recorded, and when the Pd/Pa index was reduced during the coronary spasm, the values just before the angiograms were adopted. CAG was performed immediately after coronary spasms were induced or the maximum ACh infusion was completed. If coronary spasm was induced but improved spontaneously, SPT of the left coronary artery (LCA) was performed without intracoronary injection of NTG into the RCA. In such cases, once the SPT for the LCA was completed, CAG was repeated following an NTG injection into the RCA. If the coronary spasm provoked by ACh infusion into the RCA was prolonged or severe enough to induce hemodynamic instability, an intracoronary injection of 0.3 mg) was administered to relieve spasms. Subsequently, SPT of the LCA was performed. In the LCA SPT, a pressure wire was advanced into the distal segments of the left anterior descending coronary artery (LAD) immediately after the second pressure calibration at the LCA ostium. SPT was performed by infusing 50 and 100 μg doses of ACh into the LCA using a similar method. If coronary spasm was not induced by 100 μg ACh, a maximum of 200 μg ACh was infused into the LCA. CAG was performed just after a coronary spasm was provoked or the maximum ACh infusion was completed. An intracoronary injection of 0.3 mg NTG was administered, followed by the final CAG for the LCA. In this study, low, moderate, and high doses of ACh were considered to be 20, 50, and 80 μg for RCA, respectively, and 50, 100, and 200 μg for LCA, respectively.

The minimal Pd/Pa index in response to each ACh dose was recorded, and when the Pd/Pa index was reduced during the coronary spasm, the values just before the angiograms were adopted. The difference in Pd/Pa (ΔPd/Pa) during the SPT was defined as the minimal Pd/Pa minus the baseline Pd/Pa. During the period when a PrimeWire Prestige Plus Guide Wire was available, the instantaneous free-wave ratio (iFR) was measured immediately before ACh administration in some patients. In addition, FFR was also measured in patients with coronary atherosclerosis using the conventional method of intravenous administration of adenosine triphosphate[22].

We used an autoinjector, as shown previously[21]. The coronary artery diameter was measured as previously described[21]. Lesions with > 20% stenosis were defined as atherosclerotic. We also investigated the possibility of myocardial bridging (MB), which is the presence of a > 20% systolic reduction in coronary artery diameter[23]. Complications of CAG and SPT include common severe complications, such as myocardial infarction, cerebral infarction, vascular trauma requiring surgery associated with CAG, induction of coronary spasm or coronary perforation associated with a pressure wire insertion, ventricular fibrillation (Vf), pulseless ventricular tachycardia (pVT) or hemodynamic compromise requiring catecholamine administration, and atrial fibrillation associated with SPT.

Definitions of VSA-related parameters

The activity of angina pectoris, when it occurs, was classified into three patterns: resting, exertion, and both resting and exertion. In addition, cold sweats and loss of consciousness were identified as serious signs of coronary spasms. VSA was defined as > 90% narrowing of coronary arteries on angiograms when provoked, accompanied by the presence of usual chest pain and/or the presence of an ST-segment deviation on ECG[2]. Focal spasm was defined as transient vessel narrowing of > 90% within the borders of one isolated coronary segment, as defined by the American Heart Association. Diffuse spasm was defined as a 90% diffuse vasoconstriction observed in ≥ 2 adjacent coronary segments of the coronary arteries[7]. In the present study, this assessment could be applied to each coronary artery; thus, in the assessment of each patient, the endotype of coronary spasm may differ between the RCA and LCA. In the present study, Group D consisted of patients with VSA and diffuse spasm that occurred in only one or both coronary arteries, and Group F consisted of patients with VSA and focal spasm that occurred in one coronary artery, both coronary arteries, or one of the coronary arteries. Multivessel

spasms were defined as coronary spasms that occurred in ≥ 2 major coronary arteries. For multivessel spasms, we could not assess when the subsequent SPT was negative after the avoidable use of NTG[24].

In lesion analyses, for the site of coronary spasm, each coronary artery was divided into three parts (proximal, mid, and distal), and the central part of the coronary spasm was described as diffuse.

Regarding the medications taken before SPT, although coronary vasodilators were discontinued 48 h before SPT, we investigated the number of vasodilators.

Other clinical characteristics measured in the present study

Patients were asked about their current smoking status and any family history of coronary artery disease (FH-CAD) was recorded. Hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome (MtS), and chronic kidney disease were defined based on the standard definitions and are described in previous papers[25,26]. The left ventricular ejection fraction was measured using cardiac ultrasonography. In the majority of study participants (n = 80), flow-mediated dilation (FMD), as an endothelium-dependent function, and NTG-induced dilation (NID), as an endothelium-independent function, were measured as previously described[27].

Statistical analyses

Data are presented as mean ± SD or median with interquartile ranges for non-normally distributed data and non-continuous variables. Baseline characteristics of the groups were compared using Student's unpaired t-tests, Wilcoxon signed-rank tests, or χ^2 analysis, as appropriate. Multivariate regression analysis was performed to determine the factors responsible for ΔPd/Pa during the SPT. Statistical analyses were performed using the JMP version 16 (SAS Institute Inc., United States). A P value of < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

There were 54 patients (62%) in Group D and 33 (38%) in Group F. In Group D, diffuse spasm occurred in both the RCA and LAD in 32 patients, only in the LCA in 14 patients, and only in the RCA (the LCA was not assessed due to the unavoidable use of NTG) in eight patients. In Group F, focal spasm occurred both in the RCA and LCA in four patients, only in the LCA in 13 patients, in the LCA despite diffuse spasm in the RCA in seven patients, in the RCA despite diffuse spasm in the LCA in eight patients, and in the RCA (the LCA was not assessed due to an unavoidable use of NTG) in one patient. Patient characteristics are shown in Table 1. The frequency of MtS was higher in Group F than in Group F (P = 0.04). The frequency of hypertension tended to be higher in Group F than in Group D (P = 0.06). There were no significant differences in the blood chemical parameters displayed in Table 2. The NID tended to be lower in Group F than in Group D, but there was no significant difference in FMD between the two groups. Regarding the medications taken before admission, the frequency of calcium-channel blocker (CCB) consumption was significantly higher in Group F than in Group D (P = 0.01), and the frequency of long-acting nitrate consumption tended to be higher in Group F than in Group D (P = 0.05, Table 3). On CAG and SPT, the frequencies of coronary atherosclerosis (P = 0.03) and MB (P = 0.047, Table 3, P = 0.05) were significantly higher in Group F than in Group D, whereas the frequency of occurrence of multivessel spasm did not differ significantly between the two groups (Table 3). No serious complications occurred with CAG, and no coronary spasm was induced with pressure wire insertion or coronary perforation. In the SPT, no Vf or pVT occurred, but hemodynamic instability requiring catecholamine was observed in two patients (6%) in Group F and one patient (2%, P = 0.30) in Group D. Atrial fibrillation during SPT was observed in four patients (12%) in Group F and two patients (4%, P = 0.13) in Group D, but the difference was not statistically significant.

Lesion characteristics in focal and diffuse spasms

In 87 study participants, because of a small RCA (n = 6) and inability to advance a guidewire into the distal coronary artery (n = 1 in the RCA, n = 2 in the LAD, total n = 3), 165 coronary arteries were assessed for intracoronary pressure using a pressure wire, including 80 RCAs and 85 LADs). Among the 165 coronary arteries, there were 100 diffuse spasms, 34 focal spasms, and 31 negatives, including the case with unavoidable use of NTG. The lesion characteristics of diffuse and focal spasms are shown in Table 4. Coronary atherosclerosis was more frequently observed during focal spasms than during diffuse spasms (P = 0.01). The baseline Pd/Pa and iFR did not differ significantly between the two groups; however, the minimal Pd/Pa during the SPT and ΔPd/pa during the SPT were significantly lower in focal spasm than in diffuse spasm (P < 0.01, Figure 1). The ACh dose at spasm provocation differed significantly between the two groups (P = 0.03). The frequencies of subtotal/total occlusion on CAG and ST elevation on ECG were more frequently associated with focal spasms than with diffuse spasms. FFR after SPT did not differ significantly between the two groups, perhaps because the number of study participants was small. Multivariate regression analyses using the endotype of coronary spasm,

Table 1 Patients characteristics

	Group D	Group F	*P* value
No. (%)	54 (62)	33 (38)	
Age (yr)	65 ± 11	69 ± 10	0.06
Male/Female	28/26	22/11	0.18
BMI (kg/m^2)	24.4 ± 4.2	24.7 ± 3.4	0.77
Coronary risk factors (%)			
Current smoker	11 (20)	8 (24)	0.67
Hypertension	34 (63)	27 (82)	0.06
Dyslipidemia	36 (67)	19 (58)	0.39
Diabetes mellitus	10 (19)	9 (27)	0.34
Family history of CAD (%)	12 (22)	8 (24)	0.83
MtS (%)	12 (22)	14 (42)	0.04
CKD (%)	16 (30)	13 (39)	0.35

BMI: Body mass index; CAD: Coronary artery disease; CKD: Chronic kidney disease; D: Diffuse; F: Focal; MtS: Metabolic syndrome; No.: Number.

Table 2 The results of blood chemical and echographic parameters in the 2 groups

	Group D	Group F	*P* value
Blood chemical parameters			
Total cholesterol (mg/dL)	193 ± 33	202 ± 40	0.26
Triglyceride (mg/dL)	142 ± 76	143 ± 58	0.93
HDL-cholesterol (mg/dL)	57 ± 17	57 ± 17	0.99
LDL-cholesterol (mg/dL)	107 ± 25	116 ± 32	0.16
Fasting blood sugar (mg/dL)	103 ± 30	107 ± 15	0.53
Hemoglobin A1c (%)	5.8 ± 0.9	6.1 ± 0.8	0.18
C-reactive protein (mg/dL)	0.06 (0.04, 0.18)	0.07 (0.02, 0.17)	0.74
Brain natriuretic peptide (pg/mL)	16 (10, 35)	20 (10, 30)	0.92
eGFR (mL/min/1.73 m^2)	70.7 ± 14.5	67.8 ± 14.8	0.37
Echographic parameters			
LVEF on UCG (%)	66 ± 9	67 ± 6	0.61
FMD on brachial ultrasonography (%)	3.9 ± 2.8 (n = 47)	2.8 ± 3.3 (n = 33)	0.11
NID on brachial ultrasonography (%)	15.2 ± 7.5 (n = 47)	12.3 ± 5.2 (n = 33)	0.05

D: Diffuse; eGFR: Estimated glomerular filtration ratio; F: Focal; FMD: Flow-mediated dilation; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; NID: Nitroglycerin-induced dilation; UCG: Cardiac ultrasonography.

presence of coronary atherosclerosis, and dose of ACh at spasm provocation showed that focal spasm was a significant factor responsible for the reduction of intracoronary pressure during ACh provocation ($P < 0.01$, Table 5).

The representative cases of focal and diffuse spasms with intracoronary pressure are shown in Figure 2.

DISCUSSION

This study investigated the clinical characteristics of patients with VSA and focal spasm, and compared

Table 3 The results of VSA-related parameters in the 2 groups

	Group D	Group F	*P* value
Medications taken before CAG			
Calcium-channel blocker (%)	11 (20)	16 (48)	0.01
Long-acting nitrate (%)	6 (11)	9 (27)	0.05
Statins (%)	26 (48)	9 (27)	0.05
Anti-platelet therapy (%)	14 (26)	9 (27)	0.89
VSA-related symptom			
Cold sweating or syncope (%)	5 (9)	4 (12)	0.67
CAG.SPT			
Coronary atherosclerosis (%)	28 (52)	25 (76)	0.03
MB (%)	7 (13)	10 (30)	0.05
Multi-vessel spasm (%, *n*)	32 (74, 43)	19 (66, 29)	0.42

CAG: Coronary angiography; D: Diffuse; F: Focal; MB: Myocardial bridging; SPT: Spasm provocation test; VSA: Vasospastic angina.

Table 4 Lesional characteristics in the diffuse and focal spasms

	Diffuse spasm	Focal spasm	*P* value
No.	100	34	
ST elevation on ECG during SPT	6 (6)	13 (35)	< 0.01
Total or subtotal occlusion on CAG	9 (9)	9 (26)	0.02
Spastic vessels: RCA/LAD	46/54	13/21	0.43
Spasm site			
Proximal/Mid/Distal	12/57/31	5/16/13	0.58
Dose of ACh at spasm provocation			
Low (%)/Moderate (%)/High (%)	32 (32)/65 (65)/3 (3)	13 (38)/16 (47)/5 (15)	0.03
Intracoronary pressure indexes			
Baseline Pd/Pa	0.96 ± 0.05	0.95 ± 0.05	0.35
Minimal Pd/Pa	0.77 ± 0.11	0.66 ± 0.20	< 0.01
∆ Pd/Pa	- 0.19 ± 0.11	- 0.29 ± 0.20	< 0.01
iFR (*n*)	0.96 ± 0.07 (*n* = 52)	0.95 ± 0.08 (*n* = 17)	0.83
FFR (*n*)	0.85 ± 0.08 (*n* = 26)	0.80 ± 0.10 (*n* = 8)	0.18

ACh: Acetylcholine; CAG: Coronary angiography; ECG: Electrocardiogram; FFR: Fractional flow reserve; iFR: Instantaneous free-wave ratio; LAD: Left anterior descending coronary artery; No.: Number; Pd: Distal pressure; Pa: Aortic pressure; RCA: Right coronary artery; SPT: Spasm provocation test.

these characteristics with those of patients with diffuse spasm. Our data showed a higher frequency of MtS and coronary atherosclerosis in patients with VSA and focal spasms. Lesion analyses using a pressure wire showed that the reduction in Pd/Pa during SPT was significantly greater in focal spasm than in diffuse spasm, as well as a higher frequency of coronary atherosclerosis. These findings may indicate that focal spasm causes a greater degree of myocardial ischemia than diffuse spasm does.

According to several studies investigating the prognoses of focal and diffuse spasms[7,10,11], focal spasm has the worst prognosis. Sato *et al*[7] reported that the major cardiovascular events (MACE)-free rate over six years of follow-up was 92.5% in patients with focal spasm and 96.5% in those with diffuse spasm, showing that focal spasm is a factor indicating a worse prognosis. Kim *et al*[10] showed that the MACE-free rate over 2 years of follow-up was 91.8% in patients with focal spasm and 96.8% in those with diffuse spasm, and that the cause of MACE in patients with focal spasm was acute coronary syndrome, especially unstable angina (UAP). Nishimiya *et al*[11] demonstrated that the prognosis over 6

Table 5 Multivessel regression analysis for △ distal pressure/aortic pressure during spasm provocation test

Factors	F value	*P* value
Focal spasm	14.14	< 0.01
Atherosclerosis	1.38	0.24
ACh dose at spasm provocation	1.08	0.34
R^2 = 0.18		

ACh: Acetylcholine.

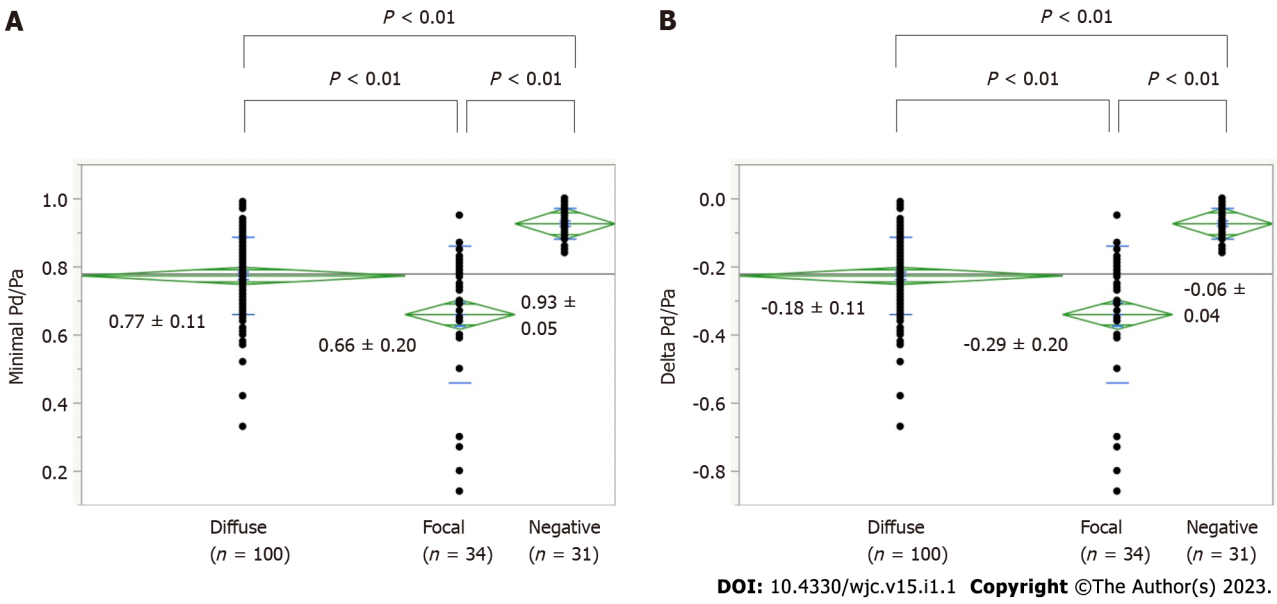

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Figure 1 The minimal distal pressure (Pd)/aortic pressure (Pa) and reduction in Pd/Pa during spasm provocation test according to the types of coronary spasm. A: Shows the minimal Pd/Pa during the spasm provocation test (SPT); B: Shows the delta Pd/Pa during the SPT in the diffuse, focal spasm, and spasm-negative vessels. In both panels, each value was lower in vessels with diffuse and focal spasms than in spasm-negative vessels (P < 0.01). Furthermore, each value was lower in vessels with focal spasms than in those with diffuse spasms (P < 0.01). Pa: Aortic pressure; Pd: Distal pressure.

years of follow-up was worse in patients with focal spasm than in those with diffuse spasm, and that the causes of MACE included nonfatal myocardial infarction and readmission for UAP or heart failure.

Several studies have used intracoronary imaging modalities for the possible mechanisms of focal spasm-induced worse prognoses[9,12-15]. Several studies using intravascular ultrasonography have demonstrated the presence of atherosclerosis at focal spastic sites[12-14]. Using optical coherence tomography (OCT), Kitano *et al*[9] demonstrated that intima area, maximum intima thickness, and lipid content were higher in focal spasm sites than in diffuse spasm sites. In a recent study using OCT, intraplaque neovessels and macrophage infiltration were also more frequently observed in focal spastic segments than in diffuse spastic segments[11]. Using coronary angioscopy (CAS), Kitano *et al*[9] also showed that atherosclerotic yellow plaques and thrombi were more frequently observed in focal spastic sites than in diffuse spastic sites. Our previous report using CAS showed that intracoronary thrombi were recognized only in focal spastic sites[15]. Taken together, these findings suggest that unstable atherosclerotic lesions may be present at the focal spastic sites. Recently, it was reported that coronary microvascular dysfunction may contribute to INOCA[28], and such coronary microvascular dysfunction was more frequently observed in coronary arteries with focal spasm than in those with diffuse spasm [22]. Such coexistence of coronary microvascular dysfunction may, in part, contribute to readmission for UAP.

In the present study, we focused on the severity of myocardial ischemia caused by focal spasms. The possibility of higher severity of myocardial ischemia by focal spasm has been demonstrated not only by ECG findings (with ST elevation) but also by the reduction of intracoronary pressure during coronary spasm induced using a pressure wire, independent of the presence of atherosclerotic lesions, spasm vessels, and the spasm segment of the coronary artery. Recently, SPT has been recommended after the assessment of microvascular function using a pressure wire[20], which shows an increase in the opportunity for SPT using a pressure wire. We hope that further studies will confirm these findings.

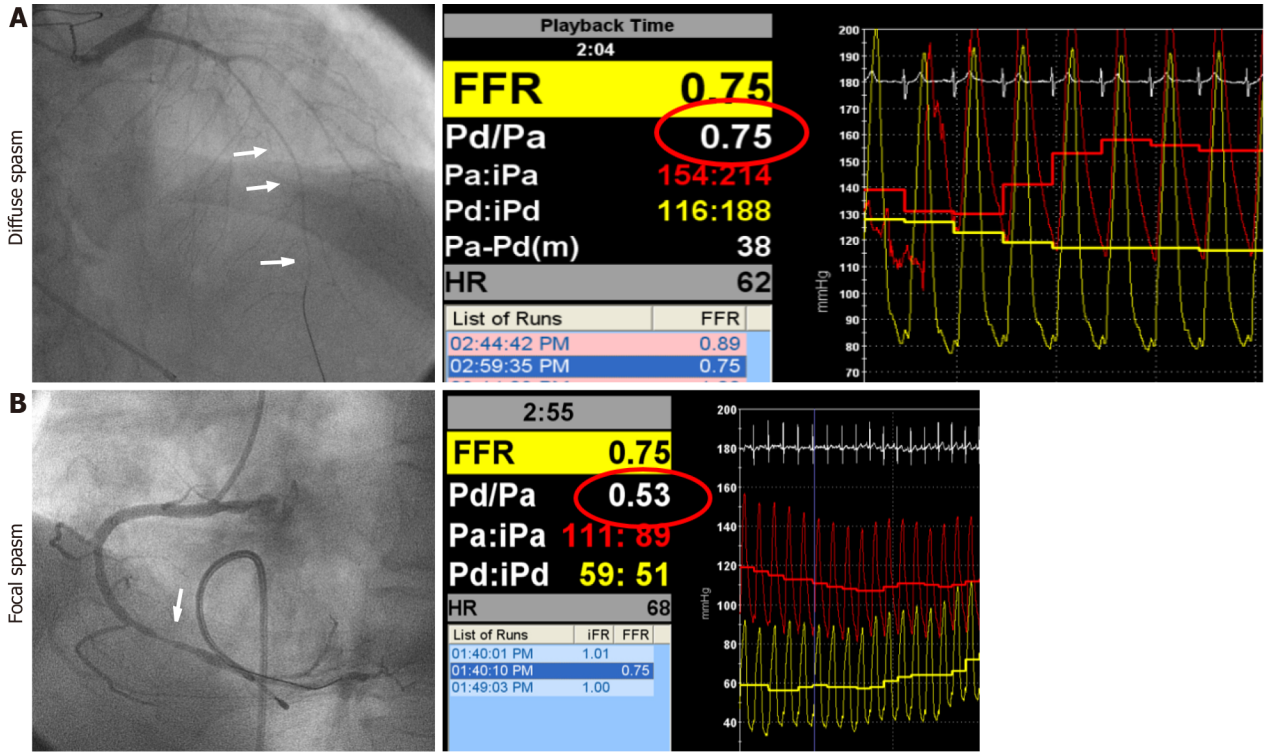

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Figure 2 The representative cases. A: Shows the presence of diffuse spasm in the left anterior descending coronary artery, and the minimal distal pressure (Pd)/aortic pressure (Pa) was 0.75; B: Shows the presence of a focal spasm on the right coronary artery, with a minimal Pd/Pa of 0.53. LAD: Left anterior descending coronary artery; Pa: Aortic pressure; Pd: Distal pressure; FFR: Fractional flow reserve.

In the present study, the dose of ACh at spasm provocation was different for focal and diffuse spasm, and Sueda *et al*[29] reported that focal spasm tends to cause coronary spasm at lower loading doses of ACh, which may be consistent with the findings of the present study. In contrast, higher doses of ACh during spasm provocation appeared to be more frequently observed in focal spasms. In the present study, the frequency of coronary dilators, such as CCB or long-acting nitrates, was high in Group F. Although we could not evaluate chest symptoms on admission in the present study, the high frequency of coronary dilator medications on admission may be due to the aim of improving chest symptoms due to the high degree of myocardial ischemia caused by focal spasm. At our institution, as per the guidelines[2], coronary dilators were discontinued 48 h prior to the SPT, but the long-acting CCB may have remained effective, resulting in higher ACh doses in the SPT in Group F.

Regarding the clinical characteristics of patients with focal spasm, it has been reported that more men than women have focal spasm[7,8]; however, our study did not confirm that more men had focal spasm. The backgrounds of the study participants may have differed slightly. Moreover, the finding of more patients with MtS and hypertension may also support the finding that patients with focal spasms had more atherosclerotic lesions. We observed a different trend of endothelium-dependent vasodilatory response in vascular endothelial dysfunction; however, it is unclear whether this is a result or a cause, and we would like to investigate this in a future study with more participants. It is still possible that there may have been a slight residual effect of the oral medication.

The implication of this study is that focal spasm may mean that the degree of ischemia is so great that effective and sufficient doses of coronary dilators should be administered. This could improve the prognosis of patients with focal spasm; however, future prospective studies are needed.

This study had several limitations. First, it was a single-center study with a small number of patients, and the results of the present examination may not be applicable to all patients with coronary spasm. Second, in classifying patients, those with both focal and diffuse spasms were assigned to the focal spasm group; however, it is unclear whether this classification is correct. Third, in this study, a pressure wire was inserted to apply a load, and it was unclear whether the insertion of the pressure wire affected the morphology of the coronary spasm. The morphology of the coronary spasm may have been affected by the insertion of a pressure wire. We also encountered a case in which it was difficult to distinguish the distal portion of a coronary spasm because of the pressure wire. Fourth, noninvasive tests such as ergonovine stress echocardiography[30] and coronary computed tomography[31,32] have been used to evaluate coronary spasm, and their usefulness has been reported; however, these tests are not routinely performed in our hospital and have not been evaluated. Fifth, we have experienced that troponin, a myocardial enzyme, is positive during severe myocardial ischemia in some VSA patients. We believe

this is an important indicator for assessing the severity of myocardial ischemia, even in VSA patients. However, at our institution, it is not routinely measured in patients with worsening chest symptoms and a long duration of attacks. Finally, the doses of ACh that induced the focal/diffuse spasms were different. Although this factor was not significant in the multivariate analysis, it may have influenced the reduction in intracoronary pressure during ACh provocation.

CONCLUSION

In conclusion, patients with focal spasm may have more atherosclerotic lesions and a greater degree of myocardial ischemia than those with diffuse spasm. Since the prognosis of patients with focal spasm has been reported to be poor, it may be necessary to administer adequate doses of coronary dilators, especially in these patients. Further prospective studies and multicenter registries are needed to clarify the need for medication.

ARTICLE HIGHLIGHTS

Research background

Coronary spasm can be divided into two types: Focal spasm and diffuse spasm, but the prognosis for focal spasm is reported to be worse than that for diffuse spasm.

Research motivation

The cause of the worse prognosis in focal spasm is unclear, and although the degree of myocardial ischemia may be more severe in focal spasm, no method has been established to evaluate the severity of coronary spasm.

Research objectives

The objective of the present study was to investigate such relationships using a pressure wire during the spasm provocation test (SPT) in patients with vasospastic angina (VSA).

Research methods

Eighty-seven patients with VSA (average age: 67 years; 50 men, 37 women) underwent SPT. During SPT, a pressure wire was advanced into the distal portion of the right coronary artery and the left anterior descending coronary artery, and the ratio of intracoronary pressure to aortic pressure (Pd/Pa) was continuously monitored. An SPT was performed with acetylcholine (ACh), and the presence of coronary spasm was defined as the presence of > 90% arterial narrowing in response to an ACh infusion, with the usual chest symptoms and/or ischemic ECG changes. Focal spasm was defined as total or subtotal spasm within one segment of the AHA classification, while diffuse spasm was defined as > 90% spasm with two or more segments. The group with focal spasm in at least one major coronary artery was classified as the focal group, and the group without focal spasm as the diffuse group.

Research results

Among 87 patients, the frequencies of metabolic syndrome and coronary atherosclerosis were higher in the focal group (n = 33) than in the diffuse spasm group (n = 54, P < 0.05). In vessel analyzes, in these 134 spastic segments, diffuse and focal spasms were detected in 100 and 34 vessels, respectively. Pd/Pa at baseline was similar in both groups (diffuse: 0.96 ± 0.05, focal: 0.95 ± 0.05, P = 0.35); however, Pd/Pa during coronary spasm was lower in focal spastic vessels (0.66 ± 0.20) than in diffuse spastic vessels (0.76 ± 0.11, P < 0.01), and the reduction in Pd/Pa during an SPT was also lower in focal spastic vessels (-0.29 ± 0.20) than in diffuse spastic vessels (-0.18 ± 0.11, P < 0.01). The presence of focal spasm was a significant factor responsible for the reduction in Pd/Pa during SPT.

Research conclusions

These findings suggest that focal spasm may be more severe than diffuse spasm, judging by intracoronary pressure during coronary spasm. This mechanism may be involved in the poor prognosis of focal spasm, and careful measures, such as intensified drug therapy, should be taken when focal spasm is detected.

Research perspectives

In recent years, more patients have been evaluated for coronary microvascular dysfunction using pressure wires and then for coronary artery spasm induced by ACh, and it is possible that pressure wires will be used more frequently to induce coronary artery spasm. It will be important to confirm the findings of this study in more cases.

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FOOTNOTES

Author contributions: Oshita C and Uchimura Y contributed to the acquisition of data and Teragawa H contributed to the writing and revision of the manuscript; All the authors approved the final version of the manuscript.

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Country/Territory of origin: Japan

ORCID number: Hiroki Teragawa 0000-0002-0183-2541; Chikage Oshita 0000-0003-3471-2543; Yuko Uchimura 0000-0001-8316-4075.

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ORIGINAL ARTICLE

Observational Study

Role of fibrinogen, albumin and fibrinogen to albumin ratio in determining angiographic severity and outcomes in acute coronary syndrome

Kunaal Makkar, Yash Paul Sharma, Akash Batta, Juniali Hatwal, Prashant Kumar Panda

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Kunaal Makkar, Yash Paul Sharma, Prashant Kumar Panda, Department of Cardiology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Akash Batta, Department of Cardiology, Dayanand Medical College and Hospital, Ludhiana 141001, Punjab, India

Juniali Hatwal, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Akash Batta, Doctor, FACC, MBBS, MD, Assistant Professor, Department of Cardiology, Dayanand Medical College and Hospital, Civil Lines, Tagore Nagar, Ludhiana 141001, Punjab, India. akashbatta02@gmail.com

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) pandemic unmasked the huge deficit in healthcare resources worldwide. It highlighted the need for efficient risk stratification in management of cardiovascular emergencies.

AIM

To study the applicability of the old, available and affordable nonconventional biomarkers: albumin and fibrinogen in their ability to predict angiographic severity and clinical outcomes in patients with acute coronary syndrome (ACS).

METHODS

In this prospective, observational study, 166 consecutive patients with ACS were enrolled. Fibrinogen, albumin and their ratio were determined from serum. Patients with underlying chronic liver disease, active malignancy, autoimmune disease, active COVID-19 infection and undergoing thrombolysis were excluded.

RESULTS

Mean age of the population was 60.5 ± 1.5 years, 74.1% being males. ST elevation myocardial infarction (STEMI) was most common presentation of ACS seen in 57% patients. Fibrinogen albumin ratio (FAR) ≥ 19.2, had a sensitivity of 76.9% and specificity of 78.9 % [area under the receiver operating characteristic curves (AUROC) = 0.8, P = 0.001] to predict ≤ thrombolysis in myocardial infarction

(TIMI) 1 flow in culprit artery in STEMI patients. Even in non-STEMI patients, FAR ≥ 18.85 predicted the same with 80% sensitivity and 63% specificity (AUROC = 0.715, P = 0.006).

CONCLUSION

Novel biomarkers, with their high cost, lack of availability and long turn over time are impractical for real-world use. Identifying ≤ TIMI 1 flow in the culprit artery has significant impact of management and outcome. Our study has shown that readily available biomarkers like fibrinogen and albumin can help identify these high-risk patients with good accuracy. This allows risk-stratification and individualization of treatment in ACS.

Key Words: Acute coronary syndrome; Albumin; Fibrinogen; Fibrinogen to albumin ratio; Total occlusion of culprit artery

Core Tip: The study highlights the role of cost-effective, readily available biomarkers fibrinogen and albumin in predicting angiographic severity and clinical outcomes in patients with acute coronary syndrome. Fibrinogen to albumin ratio independently predicted outcomes with greater accuracy compared to fibrinogen or albumin alone. Fibrinogen albumin ratio (FAR) ≥ 19.2, had a sensitivity of 76.9% and specificity of 78.9 % to predict ≤ thrombolysis in myocardial infarction 1 flow in culprit artery in ST elevation myocardial infarction (STEMI) patients. Even in non-STEMI patients, FAR ≥ 18.85 predicted the same with 80% sensitivity and 63% specificity.

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INTRODUCTION

Tremendous progress has been made in the management of acute coronary syndrome (ACS) over last six decades[1]. The success is attributed to be due to improved overall health care facilities, availability of stronger antiplatelet agents and other cardioprotective medications, improved revascularization strategies including both advances in thrombolytic therapy and the ever-improving stent design and technologies which have led to drastic decrease in morbidity and mortality associated with ACS[2-4]. However, despite the obvious progress, gaps exists and ACS continues to be the leading cause of death worldwide with considerable short and long-term mortality and morbidity. The situation is dismal in the developing world where the health care resources are scarce[5]. The coronavirus disease 2019 (COVID-19) pandemic has highlighted the same and the need for efficient triaging and risk-assessment for efficient patient management[6].

Prior to the availability of laboratory resources, the risk stratification was mainly based on the clinical assessment and accordingly clinical risk scores were developed to predict outcomes. Next, with the availability of various laboratory parameters, the risk stratification was further refined by incorporating these biomarkers. Certain novel biomarkers have been recognized ranging from C-reactive protein (CRP) to cysteine rich angiogenic inducer 61 to predict high-risk ACS[7]. Attempt has been made to incorporate these biomarkers to traditional scoring systems to add to their prognostic value, however risk stratification of ACS remains far from perfect[8]. The goal of risk stratification is not only to predict outcomes but also to guide management and more importantly urgency of treatment needed. This is even more relevant in a resource constrained setting. Hence, triaging of patients with ACS and guidance as to which patient needs early intervention and who should be managed medically is a top priority.

Starting from January 27, 2020, when the 1st case of COVID-19 was diagnosed in India, the pandemic had pushed India to the brink, stretching the already thin health care resources. It unmasked the vast deficiencies in our health care system and was a wake-up call to the country to ramp up its preparedness before the next wave. All medical and surgical specialties suffered as result, and acute cardiac care was perhaps the hardest hit[9,10]. Even before the pandemic the condition of cardiac care facilities was suboptimal and registry data of ACS from India showed that only 20% of patients of ACS undergo coronary angiography[11]. In comparison to developed nations, we have half the catheterization labs to cater to our second largest population of world[12]. The morbidity and mortality of ACS is significantly higher compared to the western world.

Novel biomarkers used to prognosticate patients often are experimental and real-world use is often not feasible[13]. Thus, we evaluated role of easily available inflammatory biomarkers like fibrinogen, albumin along with fibrinogen albumin ratio (FAR) role in ACS. They were analyzed to assess if they could predict angiographic severity or clinical outcomes among patients. The aim of the present study was to analyze the role of old, readily available biomarkers, fibrinogen, albumin and FAR in determining angiographic severity and clinical outcomes.

MATERIALS AND METHODS

Study design

This was a prospective, single center, observational study conducted between August 2019 and December 2020. Consecutive patients with ACS presenting to Cardiology department were included. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was reviewed and cleared by the Ethics committee of the Post Graduate Institute of Medical education and Research, Chandigarh (ref no INT/IEC/2019/2750). Informed written consent was obtained from all patients or appropriate legally authorized representatives.

ST elevation myocardial infarction (STEMI) was defined by patients presenting with acute chest pain and electrocardiogram showing ST elevation in ≥ 1 mm in two contiguous leads in all leads other than lead V2-V3. Cutoff point for lead V2-V3 was ≥ 2 mm in males and ≥ 1.5 mm in females[14]. Non-STEMI (NSTEMI) and unstable angina (USA) was defined as per 2014 American Heart Association/American college of cardiology non-ST elevation ACS guidelines[15]. Patients were examined by cardiologists to classify patients from Killip class 1 to 4 depending upon severity of heart failure and cardiogenic shock (CS). Patients with CS were subcategorized as per definition of Society of Cardiovascular angiography and Intervention (SCAI) into stage C to E[16]. Patients were excluded from study if they had undergone fibrinolysis, had underlying chronic liver disease, active malignancy or any autoimmune disease. Patients were followed up telephonically or in person visit at 1, 3 and 6 mo to assess their major adverse cardiovascular and cerebral events (MACCE).

Coronary angiographies were assessed by two interventional cardiologists. Culprit artery was identified by finding of angiography, 12-lead electrocardiogram and regional wall motion abnormality on echocardiography. Coronary flow was classified according to thrombolysis in myocardial infarction (TIMI) risk score[17]. Total occlusion was defined by pre percutaneous coronary artery (PCI) TIMI ≤ 1 and spontaneous recanalization (SR) was defined by TIMI score ≥ 2.

Blood sampling and lab methods

Venous blood samples were taken within 24 h of admission and prior to angiography. Fibrinogen samples were drawn in sodium citrate vacuum tubes and albumin samples in plain serum vials. FAR ratio was calculated by ratio of fibrinogen (gm/dL) and albumin (gm/dL) and multiplying the ratio by 100. Albumin levels were calculated using bromocresol method on a Technicon RA-1000 automated analyzer (Technicon Instruments, Tarrytown, NY, United States). Fibrinogen concentration was measured with turbidimetric assay using ammonium sulphate. Care was taken to ensure all samples collected were processed within 6 h of collection to ensure minimal alteration of the biomarker levels.

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, IL, United States). Variables are presented as mean ± SD or median (inter-quartile range). Variable were checked for outliers and normalcy using the Shapiro-Wilk test. Continuous variables with normal distribution were compared with the independent samples Student's *t*-test and those with non-normal distribution with the Mann-Whitney *U* test. Comparison between categorical variables was done using chi-square test or Fisher exact test. A two-sided P value < 0.05 was considered to be significant for all variables.

RESULTS

Baseline characteristics

A total of 166 patients of ACS were included in this study. The mean age of patients was 60.5 ± 10.5 years, with majority of patients being males (74%). Ninety-five (57.2%) patients presented with STEMI while NSTEMI ACS (NSTEACS) patients constituted the remaining 42.8%. Among risk factors of CAD most common was hypertension present in 63% followed by diabetes mellitus in 50% of the cohort. Rest angina was presenting complaint in over 90% patients while new onset shortness of breath was present in 18%. The mean duration of presentation to our hospital after chest pain onset was 12.8 ± 9.9 h. The mechanical complications of ACS were also assessed and patients presenting with severe left ventricular systolic dysfunction (Ejection fraction < 30%) or significant ischemic mitral regurgitation (MR) were

more common in patients with STEMI compared to NSTEACS (44.2% *vs* 21%, *P* = 0.005 and 31.6% *vs* 15%, *P* = 0.014 respectively). Patients with classical CS (SCAI stage-C) or worse was present in 26 (15.6%) patients. Angiography was done in around 88% while 62% underwent PCI. The detailed demographic details and key investigation details are presented in Table 1.

Inflammatory biomarkers

Fibrinogen levels were significantly elevated in patients with STEMI compared to NSTEMI and USA (6.3 ± 1.2 *vs* 5.3 ± 1.1 and 5.3 ± 1.3 in gm/L, respectively; *P* = 0.001). FAR was found to be significantly higher in patients with STEMI (19.1 ± 4.8) compared to NSTEMI (15.4 ± 4) and USA (15.1 ± 4.3), *P* = 0.001. Patients with significant ischemic MR and classical CS or worse at presentation had significantly higher levels of fibrinogen and FAR and lower level of albumin as shown in Table 1.

Role of biomarkers to predict outcomes

Angiography showed complete occlusion of culprit artery more commonly in patients with STEMI compared to NSTEACS 41% *vs* 21%, *P* = 0.019. Among patients with STEMI, a fibrinogen value of ≥ 6.55 gm/dL predicted TIMI ≤ 1 flow in the culprit artery with a sensitivity of 74.4% and specificity of 74.2% [area under the receiver operating characteristic curves (AUROC) = 0.805, *P* < 0.001]. FAR also predicted total occlusion of culprit artery with a higher accuracy compared to fibrinogen. A FAR value ≥ 19.2 had a 76.9% sensitivity and 78.2% specificity in predicting TIMI ≤ 1 flow in the culprit artery (AUROC = 0.808, *P* < 0.001). Similar to STEMI patients in NSTEACS too, both fibrinogen and FAR were able to predict total occlusion of culprit artery as shown in Figure 1. Fibrinogen ≥ 6.10 gm/dL had a 75.3% sensitivity and 55.6% specificity (AUROC of 0.68, *P* = 0.024) in predicting ≤ TIMI -1 flow in the culprit artery in NSTEMI patients, while fibrinogen alone was not able to predict complete occlusion in patients with USA. Likewise, FAR ≥ 18.85 predicted ≤ TIMI -1 flow in the culprit artery with a greater accuracy than fibrinogen [80% sensitivity and 63% specificity (AUROC of 0.715, *P* = 0.006)] in patients with NSTEMI. FAR ≥ 17.3 predicted < TIMI -1 flow in culprit artery with 76.4 % sensitivity and 54.3% specificity in patients with USA. Further FAR correlated with angiographic severity as determined by the SYNTAX scores. FAR increased significantly with increasing SYNTAX scores. Accordingly, the FAR values in low SYNTAX (< 22), intermediate SYNTAX (22-33) and high SYNTAX (> 33) groups were 15.8 ± 2.9, 18.4 ± 3.3 and 22.9 ± 4.2 respectively (*P* < 0.001).

The mean FAR and fibrinogen was significantly higher and mean serum albumin was significantly lower in patients with CS and significant ischemic mitral regurgitation as shown in Table 2 and Figure 2. The overall, 30-d mortality among patients of ACS was higher in patients with was 9.5% in STEMI compared to NSTEACS 2.8%, *P* = 0.004. Among inflammatory markers albumin was significantly less in patients who succumbed to illness compared to survivors (3.2 ± 0.33 *vs* 3.4 ± 0.33, *P* = 0.03). Another inflammatory biomarker assessed in our study was the CRP. CRP levels were significantly higher in non-survivors compared to survivors (56.4 ± 24.3 *vs* 35.2 ± 18.4, *P* = 0.04). However, there was no correlation of CRP with angiographic severity or the TIMI flow in our study. Thirty-day mortality of the cohort was 6.6%. MACCE occurred in 10.3% patients at a mean follow up of 6.6 ±1.5 mo.

DISCUSSION

In last sixty years, since first biomarkers of ACS were identified, their role has undergone drastic change and are now integral to management of ACS patients. They not only have a role in early diagnosis but also provide means to gain insights to underlying causes and consequences of ACS. Novel biomarkers are coming up at a rapid rate including myeloperoxidase, pregnancy-associated plasma protein-A, matrix mettaloproteinases, tissue inhibitor of mettaloproteinases, various interleukins and the novel exosomal micro RNAs[18]. However, the long turn-around time and easy accessibility besides the high cost makes them impractical for real-world use.

Pre procedural TIMI flow in culprit artery is strongly related to patient outcomes[19,20]. SR of culprit artery in STEMI patients occurs in 26% those undergoing primary PCI[21]. SR of culprit artery results from endogenous fibrinolytic system leading to dissolution of arterial thrombi. The ST resolution on 12-lead electrocardiogram is not a reliable marker to predict SR, thus necessitating the development of other biomarkers which can help in early identification of the recanalization status of the vessel and guide in patient management and prognostication[22]. Various biomarkers have been tested to predict SR; however, the results are dismal. In our study fibrinogen and FAR were able to predict total occlusion of culprit artery in STEMI with reasonably good accuracy.

The statistics on revascularization by thrombolysis or primary PCI are dismal in the country. Thrombolysis is performed in around 50% patients of STEMI while primary PCI is performed in less than 15% patients in our country[12]. COVID-19 deepened the crises further and these figures are likely to get worse during and post pandemic[6,23,24]. Moreover, the number of patients presenting late to medical facilities after STEMI are likely to increase. It has been seen that patient presenting with STEMI and occluded artery TIMI flow ≤ 1 fear worse as compared to those who have SR and benefit most from early invasive strategy[19,20]. Hence, the importance of early identification of TIMI flow in culprit

Table 1 Baseline characteristics and laboratory profile of patients with acute coronary syndrome, *n* (%)

	STEMI (*n* = 95)	NSTEMI (*n* = 38)	USA (*n* = 33)	*P* value
Risk factors				
Age, yr (mean ± SD)	61.2 ± 10.1	60.2 ± 11.0	60.5 ± 10.5	0.5
Males	73 (76.8)	25 (65.8)	25 (75.8)	0.5
Diabetes	49 (52)	20 (52.6)	14 (42.4)	0.5
Hypertension	61 (64)	22 (58)	21 (64)	0.8
Smoking	31 (32.6)	12 (31.6)	10 (30.3)	0.9
Prior history of CAD	2 (2.2)	6 (16.2)	9 (27.3)	**0.001**
Clinical features on presentation				
Rest angina	89 (93.6)	36 (94.7)	26 (78.8)	**0.013**
Ejection fraction < 30%	42 (44.2)	10 (26.3)	5 (15.2)	**0.005**
Significant ischemic MR	30 (31.6)	9 (23.7)	2 (6.1)	**0.014**
Killip class ≥ 2	24 (25.3)	7 (18.4)	2 (6)	0.057
SCAI stage C	11 (11.6)	7 (18.4)	0	**0.04**
SCAI stage D	3 (3.2)	0	0	0.3
SCAI stage E	5 (5.3)	0	0	0.14
Key investigations				
Creatinine, mg/dL (mean ± SD)	1.17 ± 0.6	1.2 ± 0.6	1.05 ± 0.47	0.42
CK-MB, (mean ± SD)	112 ± 98	71 ± 57	25 ± 24	**0.001**
Fibrinogen, gm/L (mean ± SD)	6.3 ± 1.2	5.3 ± 1.1	5.3 ± 1.3	**0.001**
Albumin, gm/dL (mean ± SD)	3.3 ± 0.33	3.4 ± 0.36	3.5 ± 30	0.075
FAR (mean ± SD)	19.1 ± 4.8	15.4 ± 4.0	15.1 ± 4.3	**0.001**

CAD: Coronary artery disease; MR: Mitral regurgitation; CK-MB: Creatinine kinase; FAR: Fibrinogen to albumin ratio; SCAI: Society of Cardiovascular angiography and Intervention; STEMI: ST elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; USA: Unstable angina.

arteries.

In NSTEACS complete occlusion of culprit artery varies from 19% to 30%. These patients are at increased risk of mortality and adverse events. Risk scoring systems and electrocardiogram are not able to identify these high-risk patients[25]. In our study similar to STEMI, both fibrinogen and FAR were able to identify patients with total occlusion in NSTEACS with reasonable accuracy. Identification of this high-risk group is rather difficult with the currently available tools. Easily accessible, readily available, cost-effective biomarkers can help better manage these patients.

High thrombus burden has remained Achilles-heel of coronary intervention since its advent in 1977 [26]. Fibrinogen being precursor of fibrin has been shown to be precursor of thrombosis, inflammatory response during ACS often leads to structural changes in fibrinogen rendering it resistant to fibrinolysis [27]. Albumin also apart from being a reflection of ongoing inflammation has pathophysiological role in thrombosis[28]. In our study only albumin amongst inflammatory biomarkers could predict short term mortality, this was similar to earlier studies showing hypoalbuminemia to be predictor of poor prognosis in patients with ACS and other cardiovascular diseases[29,30]. Thus, these inflammatory biomarkers are not merely bystanders of ongoing inflammation but have potential role in pathophysiology of ACS. The pandemic has made a call for an efficient triage system for better management of cardiac emergencies to avoid putting a strain on already this health care resources in the country. Accordingly, low risk (those who have SR) NSTEACS and STEMI should be managed medically initially while the high-risk group should receive an early invasive strategy. Using fibrinogen, albumin and their composite (FAR) could enable us to better understand and identify these high-risk ACS patients as was shown in the index study.

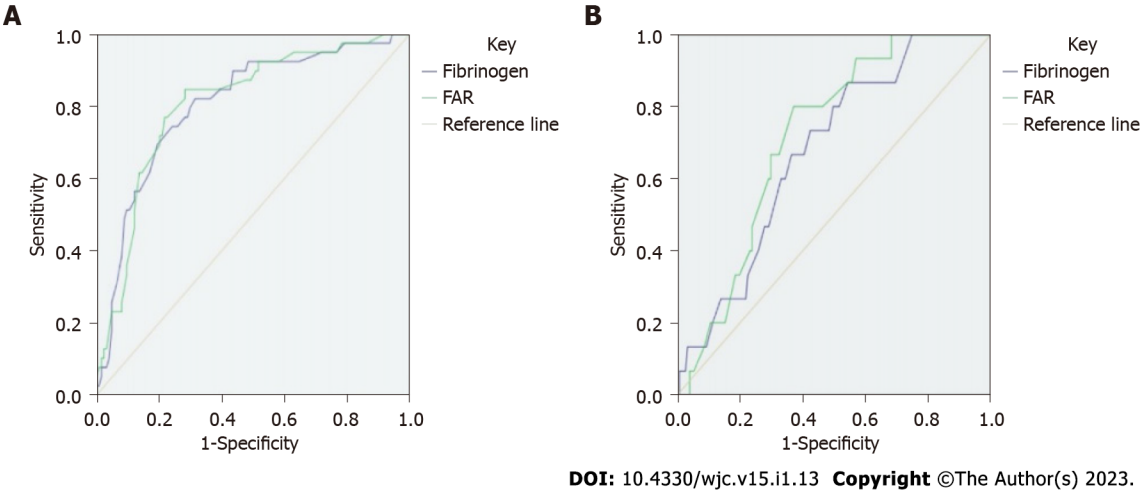
Study limitations

Our study is a single center study, with a small sample size. Thus, to generalize our results to a large population is not feasible. Serial sampling of these biomarkers was not done to assess their change in level with clinical improvement or deterioration.

Table 2 Comparison between patients with total occlusion of culprit artery compared to patients with > thrombolysis in myocardial infarction 2 flow

	Patients with TIMI- ≤ 1 flow (*n* = 54)	Patients with TIMI- ≥ 2 flow (*n* = 98)	*P* value
Age, yr	60.5 ± 10.2	60.5 ± 10.7	0.9
Time of presentation to hospital after chest pain onset (h)	13.4 ± 11.2	12.3 ± 8.8	0.24
Hypertension	33 (61)	71 (65)	0.3
Active smokers	16 (29.6)	36 (32.4)	0.3
EF < 30%	23 (42.6)	33 (29.7)	0.1
Cardiogenic shock	10 (18.5)	15 (13.5)	0.4
Complete heart block	8 (14.8)	7 (6.3)	0.07
Time to initiation of medical treatment, h	77.3 ± 63	74.5 ± 66	0.87
Time to angiography, h	107 ± 79	113 ± 141	0.84
CK-MB	101.2 ± 90	75 ± 83.4	0.11
Platelet (× 10^9/L)	1.89 ± 0.7	2.0 ± 0.91	0.17
Procalcitonin (ng/mL)	0.59 ± 0.7	1.0 ± 2.6	0.27
TLC (× 10^9/L)	10.6 ± 3.8	10.7 ± 3.9	0.8
CRP (mg/dL)	47.2 ± 34.3	39.7 ± 28.4	0.16
Fibrinogen (gm/L)	6.9 ± 1.04	5.4 ± 1.2	**0.001**
Albumin (gm/dL)	3.3 ± 0.35	3.4 ± 0.32	**0.014**
FAR	21.1 ± 3.9	15.6 ± 4.1	**0.001**

EF: Ejection fraction; CK-MB: Creatinine kinase; TLC: Total leukocyte count; FAR: Fibrinogen to albumin ratio; CRP: C-reactive protein; TIMI: Thrombolysis in myocardial infarction.

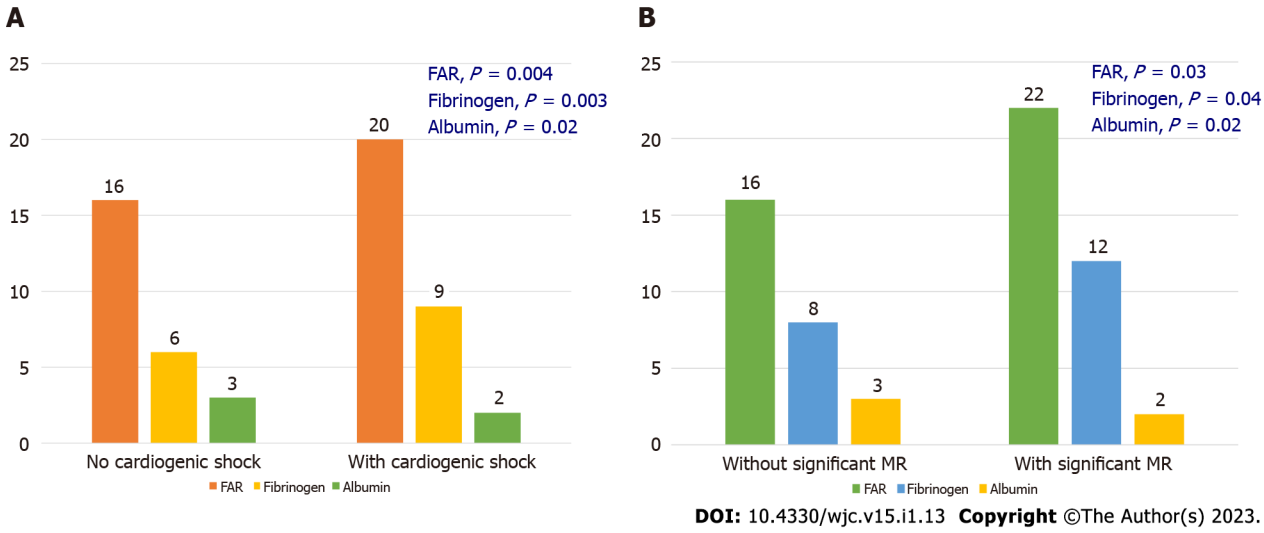


DOI: 10.4330/wjc.v15.i1.13

Figure 1 Receiver operating characteristic curve demonstrates the good accuracy of fibrinogen and fibrinogen to albumin ratio in predicting total occlusion in culprit artery. A: ST elevation myocardial infarction; B: Non-ST elevation myocardial infarction acute coronary syndrome. FAR: Fibrinogen to albumin ratio.

CONCLUSION

To efficiently manage cardiovascular emergencies in a resource constrained setting like ours, there is an ardent need to identify patients at high risk and prioritize resource allocation. Our study shows that by using old, easily available biomarkers we can effectively triage and identify this high-risk subgroup. This should pave way for further large-scale studies to affirm role of fibrinogen and FAR in predicting total occlusion of the culprit artery in patients with ACS.



DOI: 10.4330/wjc.v15.i1.13

Figure 2 Bar graphs showing the differences in mean levels of fibrinogen, albumin and fibrinogen to albumin ratio in patients. A: Patients with and without cardiogenic shock; B: Patients with and without significant ischemic mitral regurgitation. FAR: Fibrinogen to albumin ratio; MR: Mitral regurgitation.

ARTICLE HIGHLIGHTS

Research background

Despite the obvious progress in our management of acute coronary syndrome (ACS), it continues to be the leading cause of death worldwide with considerable short and long-term mortality and morbidity. The situation is dismal in the developing world where the health care resources are scarce. There is dire need for resource sensitive, readily available, realiable and easlity affordable biomarkers to enable appropriate resource allocation in cardiac emergencies.

Research motivation

The coronavirus disease 2019 (COVID-19) pandemic has highlighted the huge deficit in health care resources worldwide and made a strong case developing efficient triaging and risk-assessment for effective patient management.

Research objectives

The present study aimed to study the applicability of the old, available and affordable nonconventional biomarkers: albumin and fibrinogen in their ability to predict angiographic severity and clinical outcomes in patients with ACS.

Research methods

In this prospective, observational study, 166 consecutive patients with ACS were enrolled. Fibrinogen, albumin and their ratio were determined from serum. Patients with underlying chronic liver disease, active malignancy, autoimmune disease, active COVID-19 infection and undergoing thrombolysis were excluded.

Research results

Mean age of the population was 60.5 ± 1.5 years, 74.1% being males. ST elevation myocardial infarction (STEMI) was most common presentation of ACS seen in 57% patients. Fibrinogen albumin ratio (FAR) ≥ 19.2, had a sensitivity of 76.9% and specificity of 78.9 % [area under the receiver operating characteristic curves (AUROC) = 0.8, P = 0.001] to predict ≤ TIMI 1 flow in culprit artery in STEMI patients. Even in non-STEMI patients, FAR ≥ 18.85 predicted the same with 80% sensitivity and 63% specificity (AUROC=0.715, P = 0.006).

Research conclusions

Our study has shown that readily available biomarkers like fibrinogen and albumin and their ratio can help identify these high-risk patients with good accuracy. This allows risk-stratification and individualization of treatment in ACS.

Research perspectives

Our study makes a strong case for the readily available and cost-effective biomarkers: Fibrinogen, albumin and their ratio (FAR) to guide appropriate clinical decision making in real world setting. It

showed excellent accuracy for predictive angiographic severity and outcomes which are the most valuable piece of Information any clinician needs.

FOOTNOTES

Author contributions: Batta A, Makkar K and Sharma YP contributed conception and design; Batta A, Makkar K, Sharma YP, Panda PK and Hatwal J contributed analysis and interpretation; Batta A contributed data collection; Batta A and Makkar K contributed writing the article; Batta A, Makkar K and Sharma YP contributed critical revision of the article; Batta A and Sharma YP contributed final approval of the article; Makkar K, Panda PK and Hatwal J contributed statistical analysis; Batta A, Makkar K and Sharma YP contributed overall responsibility.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Data sharing statement: All participants gave their written informed consent for enrollment in the study. The dataset and statistical code will be made available to the readership of the journal upon reasonable request from the corresponding author.

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Country/Territory of origin: India

ORCID number: Kunaal Makkar 0000-0002-2743-6483; Yash Paul Sharma 0000-0002-1938-3377; Akash Batta 0000-0002-7606-5826; Juniali Hatwal 0000-0001-5433-0433; Prashant Kumar Panda 0000-0002-2420-5209.

Corresponding Author's Membership in Professional Societies: American college of Cardiology, No. 3445007; European society of Cardiology, No. 1036629.

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ORIGINAL ARTICLE

Prospective Study

Feasibility and efficacy of delayed pharmacoinvasive therapy for ST-elevation myocardial infarction

Rishi Sethi, Lalit Mohan, Pravesh Vishwakarma, Abhishek Singh, Swati Sharma, Monika Bhandari, Ayush Shukla, Akhil Sharma, Gaurav Chaudhary, Akshyaya Pradhan, Sharad Chandra, Varun Shankar Narain, Sudhanshu Kumar Dwivedi

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Rishi Sethi, Lalit Mohan, Pravesh Vishwakarma, Abhishek Singh, Swati Sharma, Monika Bhandari, Ayush Shukla, Akhil Sharma, Gaurav Chaudhary, Akshyaya Pradhan, Sharad Chandra, Varun Shankar Narain, Sudhanshu Kumar Dwivedi, Department of Cardiology, King George's Medical University, Lucknow 226003, Uttar Pradesh, India

Corresponding author: Akshyaya Pradhan, MD, Professor, Department of Cardiology, King George's Medical University, Shah Mina Road, Chowk, Lucknow 226003, Uttar Pradesh, India. akshyaya33@gmail.com

Abstract

BACKGROUND

ST-elevation myocardial infarction (STEMI) refers to a clinical syndrome that features symptoms of myocardial ischemia with consequent ST-elevation on electrocardiography and an associated rise in cardiac biomarkers. Rapid restoration of brisk flow in the coronary vasculature is critical in reducing mortality and morbidity. In patients with STEMI who could not receive primary percutaneous coronary intervention (PCI) on time, pharmacoinvasive strategy (thrombolysis followed by timely PCI within 3-24 h of its initiation) is an effective option.

AIM

To analyze the role of delayed pharmacoinvasive strategy in the window period of 24-72 h after thrombolysis.

METHODS

This was a physician-initiated, single-center prospective registry between January 2017 and July 2017 which enrolled 337 acute STEMI patients with partially occluded coronary arteries. Patients received routine pharmacoinvasive therapy (PCI within 3-24 h of thrombolysis) in one group and delayed pharmacoinvasive therapy (PCI within 24-72 h of thrombolysis) in another group. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 d of the procedure. The secondary endpoints included major bleeding as defined by Bleeding Academic Research Consortium classification, angina, and dyspnea within 30 d.

RESULTS

The mean age in the two groups was comparable (55.1 ± 10.1 years *vs* 54.2 ± 10.5 years, P = 0.426). Diabetes was present among 20.2% and 22.1% of patients in the routine and delayed groups, respectively. Smoking rate was 54.6% and 55.8% in the routine and delayed groups, respectively. Thrombolysis was initiated within 6 h of onset of symptoms in both groups (P = 0.125). The mean time from thrombolysis to PCI in the routine and delayed groups was 16.9 ± 5.3 h and 44.1 ± 14.7 h, respectively. No significant difference was found for the occurrence of measured clinical outcomes in the two groups within 30 d (8.7% *vs* 12.9%, P = 0.152). Univariate analysis of demographic characteristics and risk factors for patients who reported MACCE in the two groups did not demonstrate any significant correlation. Secondary endpoints such as angina, dyspnea, and major bleeding were non-significantly different between the two groups.

CONCLUSION

Delayed PCI pharmacoinvasive strategy in a critical diseased but not completely occluded artery beyond 24 h in patients who have been timely thrombolyzed seems a reasonable strategy.

Key Words: Coronary artery disease; ST-elevation myocardial infarction; Primary percutaneous coronary intervention; Pharmacoinvasive strategy; Thrombolysis; Atherosclerosis

Core Tip: Pharmacoinvasive strategy with percutaneous coronary intervention (PCI) within 3 to 24 h after successful thrombolysis has been proven to be a viable alternative to primary PCI. In resource poor countries, patients often present to the interventionist beyond 24 h of thrombolysis due to logistic reasons. The results of this study demonstrate that the clinical outcomes of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) are comparable to those of routine pharmacoinvasive (3-24 h of initiation of thrombolysis) in patients with acute ST-elevation myocardial infarction (STEMI). Hence, in critically diseased acute STEMI patients who have been timey thrombolysed, delayed PCI (24-72 h following thrombolysis) appears a reasonable strategy.

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INTRODUCTION

ST-elevation myocardial infarction (STEMI), a potentially lethal diagnosis, refers to a clinical syndrome that encompasses symptoms of myocardial ischemia with consequent ST-elevation on electrocardiography and an associated rise in cardiac biomarkers. Rapid restoration of brisk flow in the coronary vasculature is critical in reducing mortality and morbidity. Primary percutaneous coronary intervention (PCI) is the global standard of care for patients presenting with acute STEMI[1,2]. However, the practicality of all patients reaching the PCI-capable center within 1 h is a challenge. Thus, in patients with acute STEMI who cannot get primary PCI in a timely manner, pharmacoinvasive strategy is considered as an effective and viable option[3,4]. This is particularly true in developing nations where this delay often crosses the golden period of 24 h due to the exponentially increasing disease burden and limited availability of resources. The famous Occluded Artery Trial (OAT), failed to show any advantage of performing PCI (beyond 72 h) + optimal medical therapy compared to optimal medical therapy alone[5].

Therefore, in the present study we analyzed a novel concept of 'delayed pharmacoinvasive therapy' in acute STEMI patients with partially occluded coronary vasculature who had received thrombolysis within the first 12 h of symptoms onset and underwent PCI in a window period of 24-72 h, and compared both routine and delayed pharmacoinvasive strategies in such patients.

MATERIALS AND METHODS

This was a physician-initiated, single-center prospective registry which enrolled STEMI patients who were thrombolyzed within 12 h of symptom onset and subsequently underwent PCI between January 2017 and July 2017. The study protocol was approved by the local Institutional Review Board and was performed in accordance with Declaration of Helsinki. Written informed consent was obtained from all patients or from their designees before enrollment.

The enrolled patients with STEMI were either admitted to peripheral hospitals, thrombolyzed, and referred to us; or else were directly admitted to our hospital but could not undergo primary PCI and thus received thrombolysis. For various nonspecific reasons, some of them could not undergo PCI within 3-24 h of initiation of thrombolytic therapy. The common reasons for this delay were financial constraints and imbalance between the service seekers and providers which does not support 24 h functioning of catheterization laboratory, even in tertiary care centers. The period of 24-72 h has remained a grey area for the decision of primary PCI in the literature but is one of the usually encountered strategy in low resource clinical setup and used in many centers with PCI, if vessels are still found to be occluded on angiography. We called this group as delayed pharmacoinvasive group. To evaluate the effectiveness of this strategy, we compared the results with those obtained in the cohort who underwent routine pharmacoinvasive therapy (thrombolyzed within 12 h of symptom onset followed by PCI within 3-24 h initiation of thrombolysis). The groups were not randomized. Stated simply, Group 1 (routine) represented those patients undergoing PCI < 24 h of symptom onset and Group 2 (delayed) consisted of those subjects undergoing PCI between 24-72 h of symptom onset.

Patients who underwent primary PCI were excluded from the study. Other exclusion criteria included contraindication for thrombolysis, patients presenting beyond the window period for thrombolysis, or patients with totally occluded arteries on angiogram within 24-72 h.

Clinical endpoints and definitions

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 d that included composite of death, rehospitalization due to reinfarction and congestive heart failure, target vessel revascularization, and stroke. The secondary endpoints included individual primary endpoints, major bleeding as defined by Bleeding Academic Research Consortium classification, and angina and dyspnea within 30 d. The impact of time of thrombolysis to PCI on the clinical outcome (< 24 h, 24-48 h, and 48-72 h) was also assessed.

Statistical analysis

The statistical review of this study was performed by a biomedical statistician from King George's Medical University. All the data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows version 20.0; Chicago, IL, United States). Categorical and continuous variables are summarized as frequency (percentage) and the mean ± SD, respectively. The difference between groups was verified using Chi-square test for categorical variables and independent sample *t*-test for continuous variables. $P < 0.05$ was considered statistically significant.

RESULTS

The flow chart of selection of study patients is demonstrated in Figure 1. Among 880 STEMI patients who presented at our tertiary care center in the given period, 337 were divided into two groups: (1) 183 patients in the routine group who underwent PCI within 3-24 h of initiation of thrombolysis; and (2) 154 patients in the delayed group who underwent PCI within 24-72 h of initiation of thrombolysis.

Demographic characteristics of the study cohorts (routine group *vs* delayed group) are compared in Table 1. Mean age in the two groups was comparable (55.1 ± 10.1 years *vs* 54.2 ± 10.5 years, $P = 0.426$), with a predominance of male patients in both groups (87.4% in routine group and 89.6% in delayed group). The occurrence of anterior wall STEMI and non-anterior STEMI was almost equally distributed in the routine and delayed groups (53.6% *vs* 57.1% and 46.4% *vs* 42.9%; $P = 0.509$, respectively). In both groups, around 58% of patients had single vessel disease while 42% had multiple vessel disease. A statistically significant difference was noted in mean left ventricular ejection fraction between the two groups (routine: 46.9 ± 4.7 and delayed: 45.8 ± 4.5; $P = 0.034$).

In both the routine and delayed groups, thrombolysis was initiated within 6 h of onset of symptoms (5.2 ± 3.4 h *vs* 5.8 ± 4.5 h, $P = 0.125$). The mean time from thrombolysis to PCI was 16.9 ± 5.3 h in the routine group while it was 44.1 ± 14.7 h (an average 27 h late) in the delayed group.

The clinical outcomes within 30 d of the procedure in the two groups are depicted in Table 2. The primary endpoint. *i.e.*, MACCE, was reported in 16 (8.7%) patients in the routine group and in 20 (12.9%) patients in the delayed group ($P = 0.152$). Angina occurred in 4 (2.2%) patients in the routine group and in 1 (0.6%) in the delayed group ($P = 0.381$). Dyspnea occurred in 6 (3.3%) and 5 (3.2%) in the routine and delayed groups, respectively ($P = 0.99$).

Table 1 Comparison of baseline characteristics of the two study groups (mean ± SD)

Characteristic	Routine (*n* = 183)	Delayed (*n* = 154)	*P* value
Age, years	55.1 ± 10.1	54.2 ± 10.5	0.426
Age group, *n* (%)			
20–29 yr	0	2 (1.3)	0.197
30–39 yr	13 (7.1)	10 (6.5)	
40–49 yr	38 (20.8)	34 (22.1)	
50–59 yr	47 (25.7)	52 (33.8)	
60–69 yr	71 (38.8)	43 (27.9)	
70–79 yr	14 (7.7)	13 (8.4)	
Gender, *n* (%)			
Male	160 (87.4)	138 (89.6)	0.533
Female	23 (12.6)	16 (10.4)	
Risk factors, *n* (%)			
Diabetes	37 (20.2)	34 (22.1)	0.677
Hypertension	49 (26.8)	43 (27.9)	0.814
Smoking	100 (54.6)	86 (55.8)	0.825
Killip class, *n* (%)			
Class 1	165 (90.2)	129 (83.8)	0.176
Class 2	11 (6.0)	10 (6.5)	
Class 3	5 (2.7)	10 (6.5)	
Class 4	2 (1.1)	5 (3.2)	
Left ventricular ejection fraction (%)	46.9 ± 4.7	45.8 ± 4.5	0.034
Type of myocardial infarction, *n* (%)			
AWMI	98 (53.6)	88 (57.1)	0.509
Non-AWMI	85 (46.4)	66 (42.9)	
Type of coronary artery disease, *n* (%)			
SVD	105 (57.4)	89 (57.8)	0.939
MVD	78 (42.6)	65 (42.2)	
Symptoms to needle time, h	5.2 ± 3.4	5.8 ± 4.5	0.125
Thrombolysis to PCI time, h	16.9 ± 5.3	44.1 ± 14.7	0.001

AWMI: Anterior wall ST segment elevation myocardial infarction; Non-AWMI: Non-anterior wall ST segment elevation myocardial infarction; SVD: Single vessel disease; MVD: Multi-vessel disease; PCI: Percutaneous coronary intervention.

To analyze the effect of time from thrombolysis to PCI on clinical outcomes, we further divided the delayed group into two subgroups based on the time from thrombolysis to PCI: (1) 24-≤ 48 h (*n* = 96); and (2) 48-72 h (*n* = 58). The two subgroups were both compared with the routine group (thrombolysis to PCI time < 24 h; *n* = 183). However, no statistically significant difference was observed in measured clinical outcomes among the three groups (Table 3).

Univariate analysis of demographic characteristics and risk factors for patients who reported MACCE in the two groups are outlined in Table 4. A significant correlation was reported between Killip class II and the occurrence of primary outcomes in the routine group (odds ratio: 4.59; 95% confidence interval: 1.08-19.40).

Table 2 Outcomes based on primary and secondary endpoints in the two study groups

Clinical outcome	Routine (*n* = 183)	Delayed (*n* = 154)	*P* value
Primary endpoints, *n* (%)			
MACCE	16 (8.7)	20 (12.9)	0.152
Secondary endpoints, *n* (%)			
Death	5 (2.7)	3 (1.9)	0.732
Myocardial infarction	2 (1.1)	7 (4.5)	0.085
Target vessel revascularization	3 (1.6)	3 (1.9)	0.999
Congestive heart failure	6 (3.3)	7 (4.5)	0.547
Stroke	0	0	0.999
Angina	4 (2.2)	1 (0.6)	0.381
Dyspnea	6 (3.3)	5 (3.2)	0.999
Major Bleeding[1]	1 (0.5)	3 (1.9)	0.335

[1]As defined by Bleeding Academic Research Consortium (BARC) classification.
MACCE: Major adverse cardiac and cerebrovascular events.

Table 3 Outcomes based on primary and secondary endpoints among study groups

	Routine	Delayed		*P* value		
	Group A (≤ 24.0 h), *n* = 183	Group B (24.0 ≤ 48.0 h), *n* = 96	Group C (48.0–72.0 h), *n* = 58	Group A *vs* Group B	Group A *vs* Group C	Group B *vs* Group C
Primary outcomes, *n* (%)						
MACCE	16 (8.7)	13 (13.5)	7 (12.06)	0.212	0.263	0.965
Secondary outcomes, *n* (%)						
Death	5 (2.7)	2 (2.1)	1 (1.7)	0.999	0.999	0.999
Myocardial infarction	2 (1.1)	3 (3.1)	4 (6.9)	0.343	0.093	0.427
Target vessel revascularization	3 (1.6)	2 (2.1)	1 (1.7)	0.999	0.999	0.999
Congestive heart failure	6 (3.3)	6 (6.3)	1 (1.7)	0.245	0.999	0.256
Stroke	0	0	0	-	-	-
Major bleeding[1]	1 (0.5)	1 (1.0)	2 (3.4)	0.999	0.145	0.557

[1]As defined by Bleeding Academic Research Consortium (BARC) classification.
MACCE: Major adverse cardiac and cerebrovascular events.

DISCUSSION

Primary PCI within 1 h of symptom onset is the standard of care strategy in acute STEMI[1,6]. However, the real world scenarios are not always ideal, thus decision making in such cases is a challenge for interventional cardiologists[7-10]. *As per* guidelines, pharmacoinvasive therapy (thrombolysis followed with PCI within 3-24 h) is recommended as an effective option in patients with acute STEMI who could not receive primary PCI within this golden hour[6]. Furthermore, there is a lacuna in the literature regarding the role of PCI, in patients who present in a window of 24-72 h of thrombolysis. This period is critical and the benefits of reperfusion of partially occluded artery must be balanced against the potential harm from procedure-related complications, myocardial injury because of distal embolization of athero-thrombotic debris, and loss of recruitable collateral flow to other coronary territories[11,12]. In our study, we compared the effectiveness of routine (PCI within 24 h of thrombolysis) and delayed (PCI within 24-72 h of thrombolysis) pharmacoinvasive therapies and the results revealed no statistically significant difference in the clinical outcome between two therapies within 30 d of the procedure.

Table 4 Univariate analysis for prediction of primary endpoints as a measure of outcome

Variable	Events (16/183)	Routine (3-24 h)	Events (21/154)	Delayed (> 24 h)
		OR (95%CI)		OR (95%CI)
Age (> 65 yr)	1/16	0.68 (0.08-5.48)	3/18	1.31 (0.34-4.98)
Age (55-65 yr)	9/81	1.70 (0.62-4.77)	8/47	1.48 (0.57-3.86)
Age (45-55 yr)	1/41	0.21 (0.03-1.65)	5/56	0.50 (0.17-1.46)
Age (35-45 yr)	4/38	1.30 (0.40-4.30)	4/26	1.19 (0.36-3.87)
Age (< 35 yr)	1/7	1.79 (0.20-15.86)	1/7	1.06 (0.12-9.26)
Male	15/160	2.28 (0.29-18.10)	17/138	0.42 (0.12-1.46)
KILLIP Class-1	13/165	0.43 (0.11-1.67)	17/132	0.67 (0.20-2.20)
KILLIP Class-2	3/11	4.59 (1.08-19.40)	1/9	0.78 (0.09-6.59)
AWMI	9/99	1.10 (0.39-3.09)	10/88	0.64(0.25-1.61)
Type 2 DM	3/37	0.9 (0.24-3.35)	2/34	0.33(0.07-1.50)
Smoking	10/100	1.43 (0.50-4.10)	14/86	1.69 (0.64-4.47)
HTN	4/49	0.90 (0.28-2.95)	4/43	0.57 (0.18-1.79)
LVEF (35-45)	3/70	0.34 (0.09-1.25)	7/73	0.51 (0.19-1.34)
LVEF (> 45)	12/112	2.01 (0.62-6.50)	14/78	2.16 (0.82-5.68)
MVD	7/78	1.05 (0.37-2.96)	11/65	1.61 (0.64-4.05)
SVD	9/98	1.13 (0.40-3.17)	10/87	0.66 (0.26-1.66)
CrCl (30-60)	1/29	0.33 (0.04-2.61)	5/30	1.35 (0.45-4.03)
CrCl (60-90)	11/113	1.40 (0.47-4.22)	11/78	1.08 (0.43-2.72)
CrCl (> 90)	4/40	1.21 (0.37-3.99)	5/42	0.81 (0.28-2.37)

AWMI: Anterior wall ST-elevation myocardial infarction; DM: Diabetes mellitus; HTN: Hypertension; LVEF: Left ventricular ejection fraction; MVD: Multi-vessel disease; SVD: Single vessel disease; CrCL: Creatinine clearance.

Almost a decade ago, OAT-trial was published to test whether opening a totally occluded infarct related artery, 3-28 d following acute STEMI, will improve the clinical outcome or not. The results of that trial cautioned about a trend towards excess non-fatal re-infarction when PCI was performed in stable patients with a totally occluded infarct related artery, 3 to 28 d after STEMI, and did not show any reduction in major cardiovascular events during a mean follow-up of 3 years among these patients[5, 13]. Furthermore, in an analysis from the Melbourne Interventional Group registry of 4307 patients with STEMI who underwent PCI, no mortality hazard was reported where PCI was delayed beyond the first 24 h but was performed within the index admission. However, they have not defined/specified the index admission in terms of time/hours[14].

A meta-analysis of ten randomized controlled trials on timing of PCI in non-STEMI patients showed no reduction in death or re-infarction rate in early *vs* delayed intervention. However, recurrent ischemia and length of stay were significantly reduced with an early invasive strategy[15]. In non-STEMI cases, a delayed invasive approach is recommended, with an early invasive strategy within 24 h in high-risk patients and a delayed invasive strategy within 72 h in intermediate risk patients[16]. As randomized controlled trials of these kinds are difficult to plan for STEMI patients, decisions must be based on observational studies or clinical registries. Recently, a randomized controlled trial was published for transient STEMI in which the outcomes of a STEMI-like approach (with an immediate invasive strategy) were compared with a non-STEMI like approach (with a delayed invasive strategy) and the results showed no difference in clinical outcomes[17].

PCI in any scenario after 72 h is not recommended as it can be more detrimental than beneficial to vascularize the myocardium which is already dead[18]. In the present study, the mean time from symptom onset to angiography was 22.0 ± 6.6 h and 49.4 ± 15.5 h in the routine and delayed groups, respectively. Contrary to this, these time windows are significantly less in the reported literature [3,19]. Notably, it is difficult to compare the triage and referral facilities between developed and developing countries. Delayed presentation was one of the most important factors in our study determining the poor primary outcomes as compared to Western data. The delay in reaching STEMI care hospital in our country is multifactorial: (1) Delay in recognition of chest symptom by patients themselves; (2) unavail-

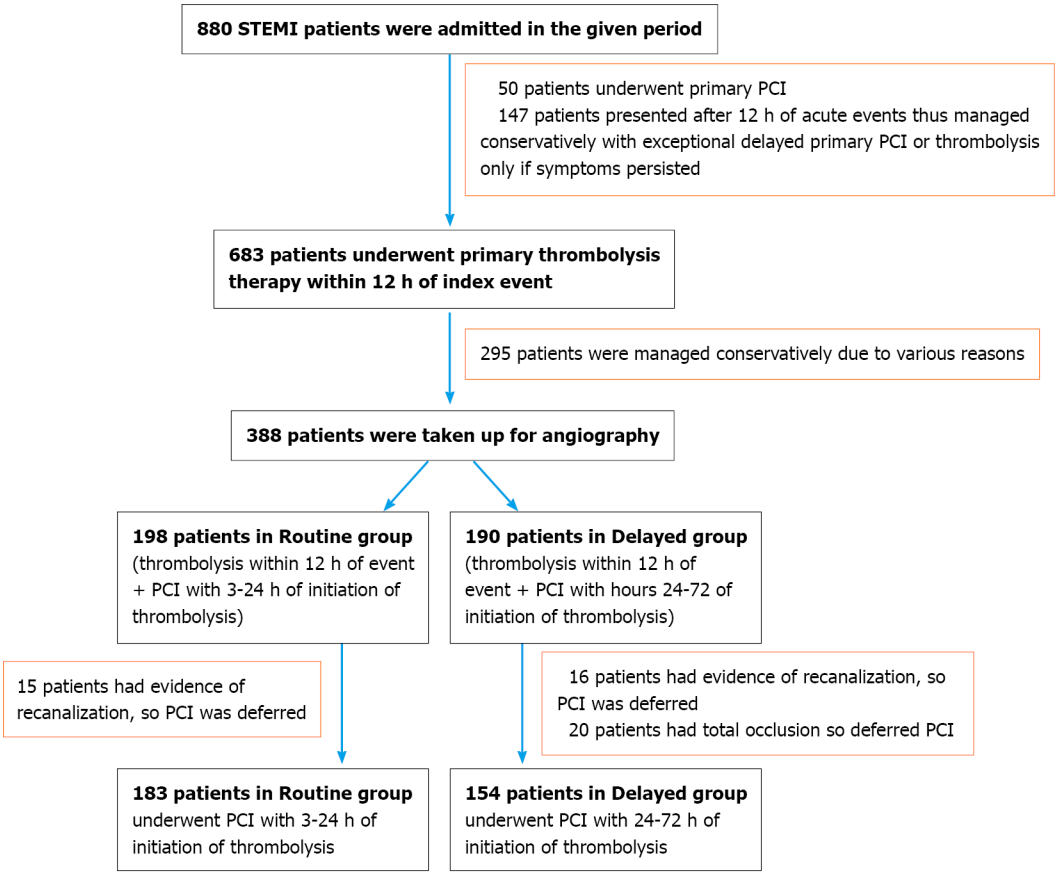

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Figure 1 Flow chart of patient enrollment in the study. STEMI: ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention.

ability of electrocardiogram machine at peripheral health care centers; (3) incompetency in diagnosing and taking decision for referral to higher centers by the health care provider; and (4) poor transportation services. However, in our opinion these loopholes in our systems are not too difficult to handle. The lag time for patient presentation can be reduced by creating public awareness regarding symptoms of acute coronary syndrome, educating the grass root level health care providers, ensuring the availability of an electrocardiogram machine at peripheral health care centers, and strengthening the ambulance services. Increasing the number of catheterization laboratories and their working hours by increasing the number of work force will also prevent the procedural delays.

The primary outcome, *i.e.*, MACCE within 30 d, was reported in 8.7% in the routine group and 13.6% in the delayed group (P = 0.152). The STEMI patients undergoing primary PCI have witnessed a wide range of MACCE (1.6% to 23.3%) with in 30 d, in various studies and variation depends on the baseline risk factors of the study population and pharmacological intervention prior to PCI[20-22]. Furthermore, in our cohort Killip class was the most important predictor of worse outcomes among all the clinical parameters analyzed by univariate analysis. Killip class II patients had larger infarct and poorer left ventricular function as compared to Killip class I and it is a well-recognized fact that the outcome of STEMI with high Killip class (≥ class II) is poor[23,24]. Male sex and left ventricular ejection fraction > 45% were the other two parameters which reported moderate significance in predicting the outcomes.

Our study is the first of its kind to clearly document the useful role of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) in patients with acute STEMI, which is extremely important and practical in low resource high burden settings.

Limitations

There were several limitations to our study. First, we enrolled a comparatively small number of patient population and had a shorter duration of the study. As randomized controlled trials are difficult to conduct in these subjects because of ethical and legal issues, keeping in mind our preliminary results which support delayed pharmacoinvasive therapy in a specified group of population, prospective registries must be encouraged to conclude further. Second, despite a prospective design, we did not use Cox proportional hazard model which has been shown to have more statistical power than logistic regression model in cross sectional studies[25]. However, when the follow-up period is short and event rates are low (as in our study), both methods may be comparable[26]. Third, we did not evaluate the psychological impact of a delayed PCI or the Post Traumatic Stress Disorder symptoms during the extra

waiting period. Fourth, despite a high rate of smoking at baseline, data regarding persistent smoking at 30 d was not available. However, counselling for smoking cessation was provided to all smokers as a protocol.

CONCLUSION

The results of the present study specifically established that the clinical outcomes of delayed pharmacoinvasive therapy (24-72 h of initiation of thrombolysis) are comparable to those of routine pharmacoinvasive (3-24 h of initiation of thrombolysis) in patients with acute STEMI. Delayed PCI (24-72 h following thrombolysis) in critical diseased but not completely occluded arteries, which have been timely thrombolysed, seems a reasonable strategy in acute STEMI patients.

ARTICLE HIGHLIGHTS

Research background

ST-elevation myocardial infarction (STEMI) when untreated is a potentially fatal condition and timely primary percutaneous coronary intervention (PCI) is the key to improving outcomes.

Research motivation

In developing countries, despite multiple guidelines and interventions, the primary PCI coverage in STEMI remains low in clinical practice. PCI within 24 h of thrombolysis (pharmacoinvasive approach) has emerged as a viable alternative to primary PCI. However, due to logistic and financial reasons, patients in developing world may undergo PCI late (> 24 h) after thrombolysis.

Research objectives

This study aimed to analyze the safety and feasibility of delayed pharmacoinvasive strategy in the window period of 24-72 h after thrombolysis. Group 1 (routine) represented those patients undergoing PCI < 24 h of symptom onset and Group 2 (delayed) consisted of those subjects undergoing PCI between 24-72 h of symptom onset.

Research methods

This was a single center, prospective registry at a tertiary care center. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) within 30 d of the procedure.

Research results

Among 337 patients with STEMI who underwent thrombolyis, there was no difference in measured clinical outcomes (MACCE) at 30 d between the routine pharmacoinvasive and delayed pharmacoinvasive groups (8.7% *vs* 12.9%, $P = 0.152$). The mean time from thrombolysis to PCI in the routine and delayed groups was 16.9 ± 5.3 h and 44.1 ± 14.7 h, respectively.

Research conclusions

Delayed PCI pharmacoinvasive strategy in a critical diseased but not completely occluded artery beyond 24 h in patients who have been timely thrombolyzed seems a reasonable strategy.

Research perspectives

Late PCI after thromobolysis in STEMI is common in developing world due to logistic and financial reasons. This study demonstrates the safety and feasibility of such delayed pharmacoinvasive PCI, lending credibility to this approach utilized in daily practice.

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FOOTNOTES

Author contributions: Sethi R and Mohan L conceived the project; Pradhan A, Vishwakarma P, Singh A, and Mohan L were involved in data collection; Shukla A, Bhandari M, Sharma S, and Chaudhary G analyzed the data; Pradhan A and Mohan L performed the literature search; Pradhan A and Sethi R drafted the manuscript; Narain VS, Dwivedi

SK, and Chandra S critically reviewed the manuscript; Sethi R, Mohan L and Pradhan A prepared the final manuscript; Sethi R and Pradhan A submitted the initial version; Sethi R, Pradhan A, and Vishwakarma P revised the manuscript; Pradhan A and Vishwakarma P prepared the rebuttal; Pradhan A submitted the revised version.

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Country/Territory of origin: India

ORCID number: Rishi Sethi 0000-0002-6745-6235; Lalit Mohan 0000-0002-4449-604X; Pravesh Vishwakarma 0000-0003-4454-2189; Abhishek Singh 0000-0003-0494-4220; Swati Sharma 0000-0002-3174-3769; Monika Bhandari 0000-0002-4699-8633; Ayush Shukla 0000-0001-9822-5459; Akhil Sharma 0000-0002-5798-5889; Gaurav Chaudhary 0000-0001-7222-9443; Akshyaya Pradhan 0000-0002-2360-7580; Sharad Chandra 0000-0002-1655-6965; Varun Shankar Narain 0000-0001-6085-5674; Sudhanshu Kumar Dwivedi 0000-0003-4656-5827.

Corresponding Author's Membership in Professional Societies: American Heart Association; European Society of Cardiology.

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SYSTEMATIC REVIEWS

Takotsubo cardiomyopathy following envenomation: An updated review

Ajay K Mishra, Anu A George, Kevin John John, Pramukh Arun Kumar, Mahati Dasari, Mohammed Afraz Pasha, Michelle Hadley

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Ajay K Mishra, Michelle Hadley, Division of Cardiology, Saint Vincent Hospital, Worcester, MA 01608, United States

Anu A George, Pramukh Arun Kumar, Mahati Dasari, Department of Medicine, Saint Vincent Hospital, Worcester, MA 01608, United States

Kevin John John, Department of Medicine, Tufts Medical Center, Boston, MA 02111, United States

Mohammed Afraz Pasha, Department of Medicine, North Alabama Medical Center, Florence, AL 35630, United States

Corresponding author: Ajay K Mishra, MBBS, MD, Academic Fellow, Division of Cardiology, Saint Vincent Hospital, No. 123 Summer Street, Worcester, MA 01608, United States. ajay.mishra@stvincenthospital.com

Abstract

BACKGROUND

Takotsubo cardiomyopathy (TTC) can be diagnosed in patients presenting with clinical features of acute coronary syndrome (ACS) by using Mayo clinic criteria. Multiple precipitators have been attributed to causing TTC. Rarely it has been reported to occur following an acute envenomation.

AIM

This review describes the various patterns, mechanisms, and outcomes of envenomation induced TTC.

METHODS

In this review, we included all studies on "TTC" and "envenomation "published in the various databases before June 2022. To be included in the review articles had to have a distinct diagnosis of TTC and an envenomation

RESULTS

A total of 20 patients with envenomation induced TTC were identified. Most episodes of envenomation induced TTC were reported following a bee sting, scorpion sting, and snake envenomation. Fear and anxiety related to the sting, direct catecholamine toxicity and administration of exogenous beta-adrenergic agents have been commonly postulated to precipitate TTC in these patients. 95%

of these patients presented with a clinical picture of ACS. Most of these patients also fulfill at least 3 out of 4 criteria of Mayo clinic criteria for TTC. Echocardiographic evidence of Apical TTC was noted in 72% of patients. 94% of these patients had clinical improvement following optimal management and 35% of these patients were treated with guideline directed medications for heart failure.

CONCLUSION

Envenomation following multiple insect stings and reptile bites can precipitate TTC. Most reported envenomation related TTC has been due to bee stings and scorpion bites. Common mechanisms causing TTC were fear, anxiety, and stress of envenomation. Most of these patients present with clinical presentation of ACS, ST elevation, and elevated troponin. The most common type of TTC in these patients is Apical, which improved following medical management.

Key Words: Takotsubo cardiomyopathy; Envenomation; Mechanism; Outcome

Core Tip: Multiple envenomations following insect stings and reptile bites can cause Takotsubo cardiomyopathy. Bee stings, wasp stings, scorpion stings, snake bites, spider bites, and jellyfish stings are the commonly reported precipitators of this cardiomyopathy. Multiple mechanisms have been postulated to cause this of which fear, anxiety, and stress of envenomation are the predominant ones. Patients usually present with clinical presentation of acute coronary syndrome, ST elevation, and elevated troponin. Echocardiography commonly shows an apical pattern of cardiomyopathy. This cardiomyopathy improves with medical management.

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INTRODUCTION

Takotsubo cardiomyopathy (TTC), aka stress cardiomyopathy, is a reversible left ventricular dysfunction syndrome precipitated by multiple emotional and environmental triggers[1]. Patient with TTC presents with the clinical picture of an acute coronary syndrome (ACS) including chest pain, abnormal cardiac enzymes, and electrocardiography (EKG) following a distinct trigger or acute stress [2]. It is most commonly reported in postmenopausal women worldwide. TTC has been reported in around 2% of patients presenting with an initial diagnosis of ACS[3].

As per the Revised Mayo Clinic Criteria, TTC can be diagnosed in the presence of the following four criteria: (1) Transient left ventricular (LV) dyskinesis extending beyond a single coronary distribution, (2) Absence of acute plaque rupture or obstructive coronary artery disease, (3) New EKG abnormalities or significant troponin elevation, and (4) absence of myocarditis or pheochromocytoma[4]. Most of the time with conservative medical management recovery of LV function occurs within 21 d in up to 95% of patients[3].

While the exact mechanisms resulting in the precipitation of TTC are not fully understood, most often it has been reported following an episode of sudden physical and emotional stressors resulting in high-catecholamine states. Over the last two decades, multiple different physical stressors have been reported to precipitate TTC[3,5]. Although uncommon TTC has been reported in patients following an episode of acute envenomation[6,7]. In this narrative review, we aimed to describe the current literature on the pattern, mechanism, and outcomes of envenomation induced TTC.

MATERIALS AND METHODS

We searched the PubMed and Medline databases for the terms “TTC” and “envenomation”. We expanded our search using the names of various agents of envenomation including “snake”, and “scorpion” and “wasp” and “bee” and “spider” and “jellyfish”. We also searched in the google scholar and Reference Citation Analysis database with similar terms. We screened the references of the initially identified manuscripts for additional manuscripts. To be included in the review articles had to have a

distinct diagnosis of TTC and envenomation. Revised Mayo Clinical Criteria was used to screen for diagnosis of TTC. Envenomation had to be confirmed based on the toxidrome specific and unique to the agent. Although evidence of the absence of coronary artery disease based on cardiac catheterization was preferred, we did include reports using an alternating modality of imaging as well. All the studies published in English, including adults with an episode of recent envenomation and subsequent diagnosis of TTC were eligible to be included in this review. In this review, we included all studies published before June 2022. All the articles were independently screened by 2 different physicians. Articles lacking clinical details, opinions, comments, and letters were excluded from this review.

RESULTS

As shown in the strobe diagram a total of 37 articles were identified (Figure 1). Among these 18 articles were eligible to be included in the review. Six of these articles were on bee sting precipitating TTC, 3 articles each on snake envenomation and scorpion sting, and 2 articles each on wasp, spider, and jellyfish envenomation induced TTC. A total of 20 patients with envenomation induced TTC were reported from thirteen different countries around the world. Tables 1 and 2 describe the details of the presentation, pattern, management, and outcome in each of these envenomations. We have described the characteristics of each of these individual envenomation related TTC below.

On bee sting precipitating TTC the total number of articles identified from various databases was 10, among which 6 articles with complete patient details were eligible to be included in the study. A total of 6 patients were reported to have TTC following a bee sting[8-12] . All these patients fulfilled at least 3 of the 4 mayo criteria for TTC as shown in Table 2. The mean age of these patients was 57, and all of them were females. The most common pattern of TTC noted was an apical type (67%). The various mechanisms that were postulated to precipitate TTC episodes were an anaphylactic reaction, epinephrine injection, catecholamine storm, cytokine storm, and direct cardiotoxic effect of the venom. Treatment details were available in 4 out of the 6 patients. Beta-blockers (BB) were used in 3 patients; Angiotensin converting enzyme inhibitors (ACEI) were used in 2 patients. Good outcome was reported in 4 patients, but multiorgan failure and death by cardiac rupture was reported in 1 patient. Interestingly improvement in a patient with cardiogenic shock was reported following mechanical circulatory support and extracorporeal membrane oxygenation.

The total number of articles on wasp envenomation and TTC identified from various databases was 5, among which 2 articles were eligible to be included in the study. A total of 2 patients were reported to have TTC following wasp envenomation[12-15]. Both the patient's fulfilled at least 3 of the 4 mayo criteria for TTC as shown in Table 2. The mean age of the patients was 75 and one of them was male. An apical pattern of TTC was noted in both patients. The mechanisms postulated to precipitate TTC episodes were an anaphylactic reaction and epinephrine injection secondary to the effect of the venom. Treatment details were available for both patients. BB and ACEI were used in both patients. No mortality was reported, and both patients had clinical improvement.

The total number of articles identified from various databases describing spider bite and TTC was 4, among which 2 articles had patient details and were eligible to be included in the study. A total of 3 patients were reported to have TTC following spider envenomation[16,17]. All these patients fulfilled at least 2 of the 4 mayo criteria for TTC as shown in Table 2. The mean age of the patients was 37 and two of them were female. Details of the pattern of TTC were not available in 2 of the 3 patients. The various mechanisms that were postulated to precipitate TTC episodes were a direct cardiotoxic effect of the venom, catecholamine storm, epinephrine, and anti-venom injection. Treatment details were not available for most of the patients. BB and ACEI were used in one patient. All three patients had improvement following treatment.

Snake envenomation precipitating TTC related articles identified from databases were 4, among which 3 articles were eligible to be included in the study. A total of 3 patients were reported to have TTC following snake bite and subsequent envenomation[18-20]. All patients fulfilled at least 3 of the 4 mayo clinic criteria for TTC as shown in Table 2. The mean age of the patients was 60 and two of them were female. An apical type of TTC was noted in all patients with additional involvement of the mid left ventricle in two. Catecholamine surge secondary to emotional stress because of snake bite was thought to be the underlying pathology of TTC. Only one patient was treated with guideline directed therapy for LV dysfunction with BB, ACEI, and a diuretic, while others received supportive care. All the patients recovered completely.

Scorpion sting related TTC articles that were identified from databases were 6. Three articles were eligible to be included in our study. A total of four patients were reported to have TTC following scorpion bite related envenomation[6,7,21-23]. All patients fulfilled at least 3 of the 4 mayo clinic criteria for TTC as shown in Table 2. The mean age of the patients was 31 and the gender distribution was equal. Apical type of TTC was noted in 2 patients and basal type of TTC in the other two patients. Abnormal response to catecholamines mediated through microvascular dysfunction, alpha toxins acting on sodium channels in the autonomic center leading to sympathetic excitation and release of catecholamines as well as a massive outpouring of catecholamines were suggested to be the precip-

Table 1 Baseline demographic characteristics and presenting features of study participants demographic characteristics of study participants

Ref.	Year of publication	Country	Age	Gender	Comorbidity	Clinical presentation
Bee						
Mishra *et al*[8]	2016	USA	63	F	Unknown	Rash, diaphoresis, chest pain, dyspnea
Aono *et al*[9]	2019	Japan	87	F	Unknown	Multiple bee stings with multi-organ failure
Seecheran *et al*[10]	2021	Caribbean	48	F	None	Obtunded, somnolent
Winogradow *et al*[12]	2011	Germany	37	F	Unknown	Local itching, spreading hives
Winogradow *et al*[12]	2011	Germany	70	F	Unknown	Swelling of throat, chest pain
Ghanim *et al*[11]	2015	Israel	37	F	None	Rash, dyspnea, impaired consciousness
Wasp						
Scheiba *et al*[13]	2011	Germany	81	M	Unknown	Absent pulses, gasping, unconsciousness
Geppert *et al*[14]	2010	Germany	70	F	Unknown	Chest pain and dyspnoea
Spider						
Alexakis *et al*[16]	2015	Greece	64	F	Hyperthyroidism	Nausea, tremor, infraorbital edema, diffuse abdominal pain, lower extremity muscle cramps
Isbister *et al*[17]	2015	Australia	33	M	Unknown	Perioral paresthesia, widespread fasciculation, diaphoresis, hypersalivation, dyspnea
Isbister *et al*[17]	2015	Australia	13	F	Unknown	Localized intense pain, urinary incontinence, profuse sweating, and vomiting
Snake						
Van Rensburg *et al*[18]	2015	South Africa	58	M	None	Bilateral ptosis
Murase *et al*[19]	2012	Japan	56	F	Unknown	Swelling of left foot
Delumgahawaththa *et al*[40]	2021	Sri Lanka	66	F	Hypertension, hyperlipidemia	Central chest pain
Scorpion						
Abroug *et al*[29]	2018	Tunisia	36	F	Unknown	Pulmonary edema, shock
Abroug *et al*[29]	2017	Tunisia	45	F	Unknown	Altered level of consciousness, respiratory failure, shock
Miranda *et al*[23]	2015	Brazil	7	M	Unknown	Localized pain, vomiting, profuse sweating, dyspnea
Jain *et al*[27]	2006	India	35	M	Unknown	Mild local pain, irritation
Jellyfish						
Bianchi *et al*[24]	2011	Italy	53	F	Unknown	Chest pain, fatigue, localized intense itch
Tiong *et al*[25]	2009	Australia	26	M	Unknown	Localized pain, restlessness, agitation, palpitations

USA: United States of America, M: Male, F: Female.

itators of TTC. Among the four patients, the first patient was treated with continuous positive airway pressure and dobutamine infusion, the second patient with intravenous furosemide, and the third patient with systemic steroids along with inotropic drugs. Except for the utilization of diuretics, these 3 patients were not treated with guideline directed therapy for LV dysfunction. However, complete recovery was reported in all patients within seven days.

Regarding Jelly Fish envenomation precipitating TTC, three articles were identified from databases. Two articles with one patient each had TTC following a jellyfish envenomation[24,25]. These patients fulfilled at least 3 of the 4 mayo clinic criteria for TTC as shown in Table 2. The mean age of the patients was 40 and one of them was male. Mid ventricular ballooning was noticed in both patients, with one patient showing apical involvement as well. Precipitators of TTC in these patients were thought to be secondary to stress, venom, and excess endogenous catecholamine release. These 2 patients were not treated with any medications for guideline directed therapy for LV dysfunction. Both patients were treated symptomatically and completely recovered within a week.

Table 2 Details of diagnosis, treatment, and outcome in study participants

Ref.	Agent	Mayo criteria	Type	Mechanism	Rx	Outcome
Mishra *et al*[8]	Bee	Apical hypokinesia, LVEF – 40 to 45%; Absence of CAD; ST elevation, T wave inversion Troponin elevation	Apical	-Cytotoxic storm; -Direct cardiotoxic effects of bee venom; -Anaphylactic reaction	-ACEI; -BB	Improved
Aono *et al*[9]	Bees (Multiple)	Apical hypokinesia; Absence of CAD; ST elevation in I, II, aVl, aVf, V2 to V6 and raised Troponin	Apical			-Multi organ failure; -Death by cardiac rupture
Seecheran *et al*[10]	African Bee	Apical hypokinesia; Absence of CAD; ST elevation in V1, V2, V3, raised Troponin	Apical	-Cytokine storm; -Anaphylaxis	-ARNI; -Eplerenone; -Bisoprolol; -Dapagliflozin	Improved
Winogradow *et al* [12]	Bee	Anterior, lateral, and Posterior hypokinesia; Absence of CAD; ST elevation in VI and raised Troponin	Reverse	-	-BB; -ACEI; -Aldosterone agonist	-
Winogradow *et al* [12]	Bee	Apical wall hypokinesia; Absence CAD; VFIB	Apical	-Hypersensitivity; -Epinephrine Injection	-	-
Ghanim *et al*[11]	Bees	Basal and Mid hypokinesia; Absence of CAD; ST elevation in lateral leads and depression in anterior and inferior leads and raised Troponin	Reverse	-Catecholamine storm; -Epinephrine injection	-IABP; -VAECMO; -Adrenaline; -Norepinephrine and Dopamine	Improved
Scheiba *et al*[13]	Wasp	Apical and anteroseptal hypokinesia, LVEF – 45%; Absence of CAD; ST elevation in I, aVL, V2-V4 and Troponin elevation	Apical	-Hypersensitivity; -Epinephrine Injection	-BB; -ACEI; -Aspirin	Improved
Geppert *et al*[14]	Wasp	Apical (anterior and inferior) and anteroseptal hypokinesia (46%); Absence of CAD; ST segment elevations in the leads, V1–V3, T-negatives in leads I, aVL and V2 –V4 and raised Troponin	Apical	-Epinephrine injection	-Bisoprolol; -Ramipril; -Aspirin	Improved
Alexakis *et al*[16]	Black widow spider	Hypokinesis of the basal and middle segments of the LV wall with apical sparing, LVEF – 36%; CAG not done; T wave flattening in aVL, and Troponin elevation	Reverse	-Alpha-ladrotoxin mediated catecholamine storm; -Cytokine storm	- BB; -ACEI; -Aspirin; -Clopidogrel	Improved
Isbister *et al*[17]	Funnel web spider	Diffuse global hypokinesia with LVEF of 20%; CAG not done; Diffuse ST changes and troponin elevation	-	-Toxin; -Antivenom; -Catecholamine storm		Improved
Isbister *et al*[17]	Funnel web spider	Reduced EF- 45%; CAG not done; ST depression in the inferior and anterior leads and elevated troponin	-	-Toxin; -Antivenom; -Adrenaline	-	Improved
Van Rensburg *et al* [18]	Cape Cobra	Mid and apical LV segment hypo or akinetic, LVEF: 27%, Absent CAD; New ST elevation across anterolateral leads, subsequent EKG showing T wave inversions in anterolateral leads, raised troponin	Mid ventricular and apical; (Apical ballooning)	-Catecholamine storm; -Cytokine storm; -Catecholamine; release associated with Intensive Care Unit medication	Supportive care; Anti-snake venom administered for snake bite	Recovery of RWMA within a week (ECHO)
Murase *et al*[19]	*Gloydius blomhoffii Snake (Mamushi)*	Abnormal LV systolic function, apical akinesis, hyperdynamic basal segment of LV; No stenotic lesions noted on the CT scan; EKG changes T inversions in 1, a	Apical	-Unknown	Supportive management; No Anti snake venom	Complete recovery (ECHO); (4 d)

		VL, V1-6, raised troponin				
Delumgahawaththa *et al*[40]	*Unidentified (Possibly Russel Viper)*	Hypokinetic mid and apex of LV segments, with ballooning, LVEF: 35%; Absence of CAD; EKG changes with ST elevation in 1 and a VL, T wave inversion II, III, a VF, V 2-6, Troponin elevation	Mid LV and Apical LV	-Catecholamine storm; -Direct myocardial toxicity; -Microvascular spasm	ACEI, BB, Diuretic, single antiplatelet, statin; Anti-snake venom	Partial recovery in 1 mo and complete in 5 mo (ECHO)
Abroug *et al*[29]	*Androctonus australis*	Patient 1: Basal ballooning of left and right ventricles; CAG not done; Troponin elevation; ST depression in four precordial leads; No other causes to explain the cardiac dysfunction. Patient 2: Impaired systolic function on echocardiogram. Basal ballooning on cardiac MRI in 24 hours; CAG not done; Troponin and ProBNP elevation; No other causes to explain the cardiac dysfunction	Basal ballooning in both patients	-Catecholamine storm; -Microvascular dysfunction	-CPAP, Dobutamine infusion; -No management mentioned	Patient 1: Discharged in 5 d, MRI in one month was normal. Patient 2: Discharged in 4 d with normal LV function on repeat echocardiography examination before discharge
Miranda *et al*[23]	*Tityus serrulatus*	Apical ballooning with hypokinesia; CAG not done; ST segment elevation in V1-V3, DI and aVL; No other causes to explain the cardiac dysfunction	Apical	-Alpha toxins act on voltage-gated sodium channels causing catecholamine storm; -Cytokine storm	-IV furosemide	Day 6 - asymptomatic, discharged; Cardiac MRI in 7 mo showed complete recovery of wall motion in apical region
Jain *et al*[27]	*Mesobuthus tamulus*	Apical, apicolateral hypokinesia; CAG not done; ST segment elevationin V1-V3 and T wave inversion; Absence of other causes of cardiac dysfunction	Apical	-Catecholamine storm; -Microvascular dysfunction	-Systemic steroids, inotropic drugs;	-Improved LVEF in 7 d; -Cerebellar infarction with clinical signs
Bianchi *et al*[24]	*Pelagia noctiluca* - A common Mediterranean jellyfish	Apical akinesis with severe left ventricular dysfunction; Absence of CAG; Acute myocardial infarction including persistent ST elevation despite thrombolysis performed for symptom relief and raised Troponin	Apical and mid-ventricular	-Direct toxicity; -Catecholamine storm; -Cytokine storm	-Symptomatic management	Improved. Completely symptom free, improved LVEF in 7 d
Tiong *et al*[25]	*Carukia barnesi* - A cubozoan/box jellyfish found in Australia	Mid-ventricular stress cardiomyopathy with apical sparing; No CAG; Persistent hyperacute T waves, rise in troponin	Mid-ventricular ballooning with apical sparing	-Sympathetic overdrive; -Catecholamine storm	-Supportive with high flow oxygen, morphine; -Magnesium sulfate IV	- Improved, discharged in 3 d

aVL: Augmented unipolar lead L; aVF: Augmented unipolar lead F; LV: Left Ventricle; LVEF: Left ventricular ejection fraction; ACEI: Angiotensin converting enzyme inhibitor; BB: Beta blocker; CAD: Coronary artery disease; CAG: Coronary angiogram; ARNI: Angiotensin receptor-neprilysin inhibitor; VFIB: Ventricular fibrillation; ECHO: Echocardiography; EKG: Electrocardiogram; IV: intravenous; RWMA: Regional wall motion abnormality; CT: Computed tomography; MRI: Magnetic resonance imaging; CPAP: Continuous positive airway pressure; Pro BNP: Pro brain natriuretic peptide; IABP: Intra-aortic balloon pump; VAECMO: Veno-arterial extra corporeal membrane oxygenation.

DISCUSSION

TTC, aka stress induced cardiomyopathy, transient apical ballooning syndrome, and broken heart syndrome is a reversible cardiomyopathy that is increasingly being diagnosed in patients presenting with ACS following a triggering event, precipitator. Multiple emotional, environmental, physical, and iatrogenic triggers have consistently been reported to precipitate such events[1-3,5,26]. While multiple stressors have been known to predispose TTC, in this review article, we highlight the multiple reported cases of TTC following envenomation which has not been reviewed before. In this descriptive review, we also discuss the various mechanisms of envenomation that have been postulated to precipitate TTC in the medical literature. Envenomation and stings have various cardiac complications including vasovagal episodes, myocarditis, ACS, and TTC. In this review, we have specifically focused on their implications in the presence of TTC. As mentioned in Figure 2 multiple mechanisms have been postulated to result in sympathetic activation which ultimately precipitates the transient LV

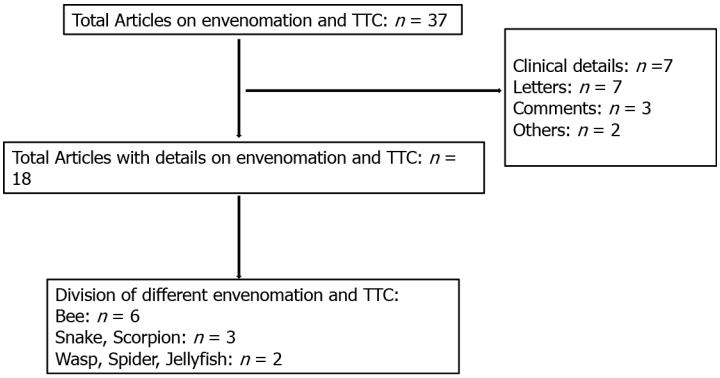

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Figure 1 Strobe diagram showing the flow of the articles. TTC: Takotsubo cardiomyopathy.

Agent	Fear/Anxiety	Cytokine storm	Direct Injury	Anaphylaxis/ Hypersensitivity	Epinephrine
Bee	+	+	+	+	+
Wasp	+	-	-	+	+
Spider	+	+	+	-	+
Snake	+	-	+	-	+
Scorpion	+	+	+	-	+
Jelly fish	+	-	+	-	-

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Figure 2 Various mechanisms precipitating takotsubo cardiomyopathy following envenomation.

dysfunction. Excessive sympathetic stimulation in these patients could be initiated by stress and subsequently worsen in the presence of another mechanism. Five distinct mechanisms have been consistently reported across the literature.

Fear, Anxiety, emotional stress

The sudden and accidental exposure to a sting or a bite that is perceived as threatening can result in peak stress. Acute emotional stress is known to increase regional cerebral blood flow in the hippocampus, brainstem, and basal ganglia and increase brain activation along with an increasing concentration of epinephrine and norepinephrine in the brain simultaneously. After an episode of acute stress, the interaction of the neocortex, limbic system, reticular activating system, brain stem, and spinal cord results in the interpretation of the stimulus as a threat. Subsequently, activation of the brainstem results in a neural stress response which results in the secretion of norepinephrine from locus coeruleus in the brain which then stimulates the hypothalamic-pituitary-adrenal axis. The sympathetic pathway through the posterior hypothalamus descends to the spinal cord and facilitates the release of norepinephrine. This increased catecholamine secretion from sympathetic nerve endings and secretion of epinephrine and norepinephrine from chromaffin cells in the adrenal medulla can subsequently affect the cardiac adrenergic receptors. Which subsequently contributes to the classical presentation of TTC. As shown in Figure 2, emotional stress was the precipitator of TTC across all the bites[18,27-29].

Cytokine storm

During an animal bite or an envenomation, venom is injected with the help of stinging apparatus into the dermal-epidermal junction, subcutaneous tissues, vessels, or muscle fibers. Venoms are chemically a diverse mixture of proteins, amines, and salts produced for predation or protection and can result in significant injury on injection to humans as well. Following the bite metalloproteinase, and L-Amino acid oxidase present in these venoms result in local dermal proteolysis, tissue destruction, and apoptosis, subsequently providing access to toxins to circulation, and target organ. Once within circulation, these toxins can alter the structure and function of endothelial cells. These agents are not only highly proinflammatory resulting in the secretion of excessive inflammatory markers they also precipitate dysregulation of neutrophils, mononuclear phagocytic system, and granulocytes thus

accelerating inflammation and cell damage. Dysregulation and excessive stimulation of these cytokines, and pro inflammatory mediators result in cytokine storm causing multiorgan dysfunction. Multiple infections [including Novel coronavirus disease 19 (COVID-19)], toxins, cancers, and diseases are known to cause TTC due to cytokine storms precipitated by endothelial dysfunction[18,30,31].

Direct catecholamine injury/toxicity

Emotional stress like pheochromocytoma is associated with an excessive outburst of catecholamine. In patients with TTC, catecholamine levels can be extremely high as compared to other cardiac diseases. Similarly, patients with TTC have been shown to have higher ventricular catecholamine sensitivity. Alpha ladrotoxin in spider venom and alpha toxin in scorpion venom has been reported to precipitate catecholamine storm. Subsequently, excessive norepinephrine released from cardiac sympathetic nerve terminals can result in a reduction of cardiac myocyte viability. Transient elevations of catecholamines in TTC result in localized focal mononuclear inflammatory cells, fibrosis, and contractions bands in cardiac myocytes. This is evident with elevated cardiac enzymes and localized areas of edema, without late enhancement in magnetic resonance imaging. Direct catecholamine injury was also commonly reported to be the precipitate TTC following all the envenomations[28,31-33].

Anaphylaxis/ Hypersensitivity

Anaphylaxis secondary to bites and envenomation is immunoglobulin E (IgE) mediated. In patients with prior sensitization, systemic reactions can occur in up to 9% of patients. Major allergens like Antigen 5, phospholipase A1, phospholipase A2, hyaluronidase, and acid phosphatase can precipitate classic Ig E mediated anaphylactic response. Subsequently, mast cells and basophils degranulate releasing proinflammatory markers including histamine and proteases. Which results in the activation, influx, and migration of neutrophils and lymphocytes and the secretion of chemokines and cytokines. Anaphylaxis induced myocardial injury can be diverse. In a study including 300 patients with anaphylaxis myocardial injury was reported in 7.3% of patients. The etiologies of myocardial injury were anaphylactic cardiomyopathy, TTC, and Kounis syndrome. The causes of excessive catecholamine release precipitating TTC in anaphylaxis are multifactorial. Histamine can stimulate the adrenal medulla directly to produce catecholamine, compensatory catecholamine release due to activation of the renin-angiotensin-aldosterone axis, and external administration of adrenaline for anaphylaxis and norepinephrine for persistent shock. This form of TTC was only reported following bee and wasp stings [3,28,31,33].

Exogenous Beta-adrenergic receptor stimulation

In normal patients beta1-adrenergic receptor (B1AR) and B2AR receptors density are highest in the apex, thus making it susceptible to exposure to higher levels of catecholamine. Following exposure to supratherapeutic doses of catecholamine signal trafficking of catecholamine receptors occurs, which is a form of protective response of cardiac myocytes to stress. This switching of Gs to Gi coupling of B2AR receptors results in reduced inotropy and apoptosis of cardiac myocytes. This supratherapeutic level of catecholamine surge is classical of pheochromocytoma thus requiring evaluation of the same and has been incorporated into the Mayo clinic criteria for diagnosis of TTC. Exogenous catecholamines have been consistently reported to precipitate TTC. TTC has been reported following the administration of epinephrine to patients subcutaneously, intravenously, and through inhalation. Iatrogenic large volume adrenaline injection has also been reported to precipitate TTC. As shown in Image 2 exogenous catecholamine injection was the second most reported mechanism of TTC after emotional stress in these patients[11-13,28,31,34-37].

Multiple other mechanisms including microvascular dysfunction and spasm, abnormal myocardial metabolism and intracellular lipid accumulation, myocardial inflammation, estrogen excess, and endothelial dysfunction have been postulated[28,31,38]. In patients with envenomation induced TTC, multiple mechanisms can initiate and precipitate cardiac dysfunction.

Clinical Profile

In this narrative review, we summarized the clinical features following envenomation induced TTC. Most insect stings and reptile bites are accidental. Following these bites and stings, clinical manifestations can vary from an asymptomatic state and mild local reactions to severe multiorgan dysfunction based on the dose and the characteristics of the venom. TTC can occur irrespective of prior cardiac comorbidities and in absence of traditional cardiac risk factors. To summarize the clinical features of these envenomations with TTC we combined the episodes of TTC following all the envenomation. To date envenomation resulting in TTC has been described in the above-mentioned animals. Almost all these patients presented with a clinical picture of ACS (95%) and had EKG changes and elevated troponin (100% each). Sixty percent of these patients had ST segment elevation (n = 12), and 15% of them had ST depression and T wave inversion simultaneously (n = 3). Among patients with echocardiographic evidence of TTC (n = 18), Apical TTC was found in 72% of patients (n = 13), reverse TTC in 28% (n = 5), and midventricular TTC was reported in 17% (n = 3) of patients. Details of Coronary angiogram (CAG) were mentioned in 85% of patients (n = 17) and all the CAG were negative for any acute

obstructive disease.

Conservative medical management was initially done on all the patients. Management was mostly physician directed and clinical feature driven. Medications for heart failure management were given to 35% (n = 7) of patients. These 7 patients were treated with ACEI, and BB together. Ionotropic agents were used in 15% (n = 3) and aldosterone agonist was used in 10% (n = 2) of patients. Details of clinical outcomes were available for 18 patients among whom 17 (94%) had clinical improvement. Improvement in LV ejection fraction (LVEF) and regional wall motion abnormality was reported in all patients with clinical improvement. Death occurred in one patient following multi organ dysfunction and cardiac rupture after multiple bee stings. As *per* the author's knowledge, this is the first review summarizing the various mechanisms, clinical features, management, and outcome following envenomation's precipitating TTC[34,35,39].

This review has a few limitations. All patients with TTC secondary to envenomation were included from case studies spanning more than a decade. Most studies did not rule out pheochromocytoma. Most of these patients did not have baseline echocardiography before admission. Studies also lacked details of CAG at presentation and echocardiographic details during follow up. Even though multiple mechanisms of TTC were considered, case studies did not report levels of inflammatory markers, catecholamine levels, IgE levels, Eosinophil counts, or advanced cardiac imaging. Most of these reports did not mention the different components of the venom which were instrumental in the precipitation of TTC[39,40]. Classification of the severity of these toxidromes, varied treatment protocols and non-availability of recurrence, functional status at discharge, and long term follow up data continue to be a challenge[3,4,26,33,33,39-41]. However, this review has the strength of describing the patterns and mechanisms of envenomation related TTC and their outcome. We also recommend that future case studies should focus on using a uniform diagnostic criterion for diagnosing and reporting TTC from episodes of stings or envenomation. Future studies should identify specific components in the venom precipitating catecholamine storm, microvascular injury, and myocardial damage[42-44]. Uniform echocardiography at diagnosis and follow up should be done consistently. All available details including imaging modalities and pattern of cardiac involvement should be consistently reported[45]. Given the rarity of these events, randomized trials on these specific etiologies might be difficult, interim optimal medical management during the envenomation and goal directed therapy for heart failure should be considered in patients who have evidence of LV dysfunction with low ejection fraction, unless complete recovery of clinical symptoms, signs, and LVEF is documented at the time of discharge from hospital. Guideline directed heart failure medications including BB and ACEI can be administered and consistent reporting of these subgroups of patients should be encouraged.

CONCLUSION

In conclusion, multiple insect stings and reptile bites related envenomation can precipitate TTC. Most envenomation related TTC has been due to bee stings and scorpion bites. Fear and anxiety related to the sting, direct catecholamine toxicity, and administration of exogenous beta-adrenergic agents have been commonly postulated to precipitate TTC in these patients. Most of these patients present with clinical presentation of ACS, ST elevation, and elevated troponin. Most of these patients also fulfill at least 3 out of 4 criteria of Mayo clinic criteria for TTC. The most common type of TTC in these patients is Apical, which improves following medical management. One third of these patients were treated with ACEI and BB with reported improvement in outcome.

ARTICLE HIGHLIGHTS

Research background

Multiple different physical, emotional and iatrogenic stressors have been known to precipitate stress induced cardiomyopathy also called takotsubo cardiomyopathy (TTC).

Research motivation

Rarely TTC has been reported in patients following an episode of acute envenomation secondary to insect stings and reptile bites.

Research objectives

This review aimed to narrate the current literature on the patterns, mechanisms, and outcomes of envenomation induced TTC.

Research methods

This review included all studies on "TTC" and "envenomation "published in PubMed, Google Scholar,

and Reference Citation Analysis databases before June 2022. Articles had to have a distinct diagnosis of TTC with Revised Mayo Clinical Criteria and documented envenomation.

Research results

Envenomation related TTC was reported from all over the world. The reports of envenomation induced TTC were reported mostly following a bee sting, scorpion sting, and snake envenomation. Fear and anxiety related to the sting, direct catecholamine toxicity, and administration of exogenous beta-adrenergic agents were postulated to precipitate TTC in these patients. Most patients presented with a clinical picture of acute coronary syndrome (ACS), ST elevation, and elevated troponin. Echocardiographic evidence of Apical TTC was noted in most of the patients. Almost all of these patients had clinical improvement following optimal management.

Research conclusions

Envenomation following multiple insect stings and reptile bites can precipitate TTC. Most reported envenomation related TTC has been due to bee and scorpion stings. Common mechanisms causing TTC following envenomation are fear, anxiety, and stress. Most of these patients present with clinical presentation of ACS. The most common type of TTC in these patients is Apical, which improved following medical management.

Research perspectives

Multiple envenomations following insect stings and reptile bites can cause TTC. Worldwide bee stings, wasp stings, scorpion stings, snake bites, spider bites, and jellyfish stings are the commonly reported precipitators of this cardiomyopathy. Multiple mechanisms have been postulated to cause this of which fear, anxiety, and stress of envenomation are the predominant ones. Patients usually present with a clinical presentation of ACS. Echocardiography commonly shows an apical pattern of cardiomyopathy. This cardiomyopathy improves with medical management.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Ajay K Mishra 0000-0003-4862-5053; Anu A George 0000-0002-6769-732X; Kevin John John 0000-0003-3382-0294; Pramukh Arun Kumar 0000-0003-3497-1334; Mahati Dasari 0000-0003-0578-8944; Mohammed Afraz Pasha 0000-0001-6629-6690.

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