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## Contents

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*MINIREVIEWS*

# Spontaneous coronary artery dissection: A review of diagnostic methods and management strategies

Nikolaos Lionakis, Alexandros Briasoulis, Virginia Zouganeli, Stavros Dimopoulos, Dionisios Kalpakos, Christos Kourek

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## Abstract

Spontaneous coronary artery dissection (SCAD) is a rare non-atherosclerotic cause of acute coronary syndromes defined as non-iatrogenic, non-traumatic separation of the coronary artery wall. The most common profile is a middle-aged woman between 44 and 53 years with few cardiovascular risk factors. SCAD is frequently linked with predisposing factors, such as postpartum, fibromuscular dysplasia or other vasculopathies, connective tissue disease and hormonal therapy, and it is often triggered by intense physical or emotional stress, sympathomimetic drugs, childbirth and activities increasing shear stress of the coronary artery walls. Patients with SCAD usually present at the emergency department with chest discomfort, chest pain, and rapid heartbeat or fluttery. During the last decades, the most common problem of SCAD was the lack of awareness about this condition which has led to significant underdiagnosis and misdiagnosis. However, modern imaging techniques such as optical coherence tomography, intravascular ultrasound, coronary angiography or magnetic resonance imaging

have contributed to the early diagnosis of the disease. Treatment of SCAD remains controversial, especially during the last years, where invasive techniques are being used more often and in more emergent cardiac syndromes. Although conservative treatment combining aspirin and beta-blocker remains the recommended strategy in most cases, revascularization could also be suggested as a method of treatment in specific indications, but with a higher risk of complications. The prognosis of SCAD is usually good and long-term mortality seems to be low in these patients. Follow-up should be performed on a regular basis.

**Key Words:** Spontaneous coronary artery dissection; Non-atherosclerotic coronary artery disease; Angiographic classification; Percutaneous coronary intervention



**Core Tip:** Spontaneous coronary artery dissection (SCAD) is a non-atherosclerotic cause of acute coronary syndromes defined as non-iatrogenic, non-traumatic separation of the coronary artery wall. During the last decades, the most common problem in SCAD was the lack of awareness of the disease which led to significant underdiagnosis and misdiagnosis. However, modern imaging techniques such as optical coherence tomography, intravascular ultrasound, coronary angiography or magnetic resonance imaging have contributed to the early diagnosis of SCAD. Although conservative treatment combining aspirin and beta-blocker remains the recommended strategy in most cases, revascularization could also be suggested as a method of treatment in specific indications.

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## INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is a rare non-atherosclerotic cause of acute coronary syndromes (ACS) defined as non-iatrogenic, non-traumatic separation of the coronary artery wall[1]. It usually occurs in young and middle-aged women with few cardiovascular risk factors. Recent studies have shown SCAD to be the underlying cause of myocardial infarction (MI) in 22%-43% of women < 50 years and approximately 21%-27% of pregnancy-associated MI[2-4]. In Canada, SCAD was responsible for 24% of women < 50 years with MI[5] while in Japan this percentage was 35%[3]. In a French series, SCAD was reported in 36% of women under 60 years with ACS and one or few conventional cardiovascular risk factors[6]. Finally, a smaller Australian registry found a prevalence of SCAD of 23% in women under 60 years presenting with ACS[7].

During the last decades, the most common problem in SCAD is the lack of awareness about this condition among healthcare providers, despite the fact that the first case report of this syndrome was a female patient back in 1931[8]. This awareness led to significant underdiagnosis and misdiagnosis in cardiology departments. However, more and more cases are now being identified due to the increased awareness and earlier use of invasive angiographic methods in patients with acute chest pain presenting to emergency departments. Modern imaging techniques such as optical coherence tomography (OCT), coronary angiography or magnetic resonance imaging (MRI) have also contributed to the early diagnosis of the disease. SCAD is not as rare as previously thought. It was supposed to be the main cause for 0.1% to 0.4% of all ACS but these percentages have increased up to 4% over the last years[2,9]. In sudden cardiac deaths, SCAD was reported in 0.5% of cases after autopsy[10]. It is frequently linked with predisposing factors, such as postpartum, fibromuscular dysplasia (FMD) or other vasculopathies, connective tissue disease and hormonal therapy, and it is often triggered by intense physical or emotional stress, sympathomimetic drugs (cocaine, amphetamines), childbirth and activities increasing the intra-abdominal and intra-thoracic pressure (coughing, retching, vomiting) and, thus, shear stress of the coronary artery walls[11].

Treatment of SCAD remains controversial, especially during the last years, where invasive techniques are being used more often and in more emergent cardiac syndromes. Conservative treatment combining aspirin and beta-blocker remains the recommended strategy in most cases. However, the high rate of technical complications in SCAD treated with primary percutaneous coronary intervention (PCI), has been shown to be associated with adverse clinical outcomes[12,13].

The aim of the present review was to demonstrate the existing knowledge regarding the diagnostic methods and the treatment strategies of the underdiagnosed syndrome of SCAD, and highlight the role of primary PCI.

## EPIDEMIOLOGY AND PATHOGENESIS OF SCAD

Although SCAD was primarily considered a disease of young adults, nowadays, the most usual patient is a middle-aged woman between 44 and 53 years with few cardiovascular risk factors[14,15]. There is evidence from a Canadian series that female patients with SCAD are older, with less isometric exercise and higher emotional stress compared to male patients[16]. Clinical presentation and outcomes of SCAD may be similar, not only in white patients, but also in other populations such as Hispanic Americans and Blacks[17]. The fact that most case reports include white patients could be explained by the fact that it may be underestimated in other populations or patients belonging in these populations may not present at the emergency department on time. Patients with SCAD usually have lower levels of hypertension, hyperlipidemia or tobacco use compared with patients who have atherosclerotic acute MI [18]. However, the prevalence of these factors is similar between different ages and sex[18]. Hypertension ranges from 32% to 37% while hyperlipidemia from 20% to 35%[14,15]. The prevalence of SCAD in patients presenting with ACS has risen up to 4% and is the underlying cause of up to 35% of all ACS cases in women ≤ 50 years[2,9].

Pregnancy has a strong association with SCAD. In pregnant women, where the percentage of SCAD-associated MI is up to 27%[4,19], dissection may be a consequence of increased physiological hemodynamic stress or high progesterone levels, leading to weakening of the coronary arterial wall[20]. SCAD episodes are presented either antepartum or post-partum, and specifically, early post-partum (within the first 6 wk of childbirth), late post-partum (from 6 wk to 1 year), and very late post-partum (1 to 2 years)[20]. The most common period of an episode is the first week after childbirth[21]. Women with post-partum SCAD tend to be older at first childbirth and multigravidas compared to non-post-partum SCAD women[21]. Hemodynamic changes affecting cardiac parameters could lead to higher levels of shear stress and, as a result, vessels including the aorta and coronary arteries present structural alterations[22].

Secondary iatrogenic dissection is also a major cause of additional risk in patients with already established SCAD undergoing invasive treatment. Increased risk of secondary iatrogenic dissections during coronary angiography (2%), non-SCAD angiography (0.2%) and PCI (14.3%) in SCAD patients has been previously observed in case series[23].

There is still a gap in the literature regarding the understanding of the potential underlying mechanism of non-atherosclerotic SCAD. Two potential theories regarding the initiation of the coronary artery wall have been proposed. The first theory indicates sudden disruption of the coronary artery wall caused by an intimal tear[24,25]. Specifically, the intimal tear results in separation of the inner intimal lining from the outer vessel wall, allowing blood to enter into the false lumen and create an intramural hematoma within or between one of the three layers (intima, media, or adventitia)[24,26]. Pressure-driven expansion of the hematoma causes propagation of the dissection plane with formation of a true lumen, and a thrombus containing a false lumen. The second theory suggests spontaneous rupture and bleeding of the vasa vasorum within the vessel wall, followed by intramedial hemorrhage[24,25,27]. Intramural hematoma (IMH), which compresses the true lumen, causes ischemia of the myocardium, being thus, the primary cause of ACS with SCAD[1]. Occlusion of the lumen may also be worsened by thrombi in the true or false lumen having, however, a small pathophysiologic role compared to IMH [28].

SCAD may affect either normal vessels or vessels with weakened arterial wall architecture due to predisposing arteriopathies. As a result, dissection of the coronary artery walls could be extensive both anterograde and retrograde[1,29,30].

## RISK FACTORS

This syndrome is mainly caused by a combination of factors including sex, hormonal fluctuations, underlying arteriopathies, genetics, and environmental, physical and emotional precipitants. As already mentioned above, pregnancy is a strong predisposing factor of SCAD in women[21]. However, a number of additional factors have been associated with the onset of SCAD in more than half of patients. Extreme physical or emotional stress is probably the most important predisposing factor. Triggering factors leading to a Valsalva-like increase in thoracoabdominal pressure or raising catecholamines, including cocaine exposure or sympathomimetic drugs, intense physical activity, coughing, retching, vomiting and bowel movement, in combination with underlying predisposing arteriopathies, can increase cardiocirculatory shear stress resulting in SCAD[11,15,31,32]. Specifically, emotional stressors seem to appear more often in women, whereas physical stressors have been reported in men among precipitants[16,29].

A significant risk factor of SCAD is FMD. The first case series of concomitant SCAD and extracoronary FMD was reported back in 2011[33]. Since then, high prevalence of FMD has been observed in 72% to 86% of SCAD patients who were routinely screened[11,34]. FMD is an idiopathic, nonatherosclerotic and noninflammatory systemic vasculopathy characterized by unique angiographic findings reflective of perturbations in the structure of the arterial wall leading to luminal stenosis, especially in small and medium-sized arteries[35]. Although the pathophysiology of FMD causing SCAD remains unknown, it is suggested that fibrosis of the vasa vasorum leads to coronary vessel wall ischemia and proliferation of myofibroblasts resulting in dissection[36]. Apart for stenoses, FMD has variable arterial manifestations including aneurysms and dissections. Multifocal FMD, characterized by multiple stenoses in an artery, is the most common type in adults, mainly affecting women. The difference between multifocal and focal FMD is that the first corresponds with medial fibroplasia, perimedial fibroplasia, and medial hyperplasia on histopathology while the second with adventitial and intimal disease[35,37]. A previous study[38] showed that the predominant arteries involved in FMD are renal (66.67%), iliac (44.44%), carotid (37.04%), and vertebral (33.33%). As a result, the prevalence of FMD may be even higher when screening is performed in patients with hypertension[38,39]. FMD and SCAD are directly associated, as prevalence of FMD among patients with SCAD is > 50%[40,41].

Long-term exposure to exogenous estrogen or progesterone has been shown to cause long-term changes in coronary arterial architecture, being thus, a significant risk factor for SCAD[11].

A relation between systemic inflammation and SCAD seems to exist[42]. Frequent chronic inflammatory systemic diseases including systemic lupus erythematosus, inflammatory bowel disease and sarcoidosis are suggested to have a potential relationship with SCAD[43-45]. A potential vasculitic inflammatory mechanism could be the activation of eosinophils from the adventitial and peri-adventitial layers a mechanism which leads to the establishment of SCAD[46]. There are data supporting this hypothesis which shows the presence of peri-arterial eosinophils in patients with SCAD compared to patients with iatrogenic or traumatic dissections where eosinophils are absent[47].

Specific connective tissue disorders such as Marfan and Ehler-Danlos type 4 syndromes also seem to have a relation with SCAD, with a reported frequency between 1% and 2%[11]. Some connective tissue disorders such as Marfan syndrome are associated with mutations in a single gene (FBN1), whereas others such as hypermobility type Ehlers–Danlos syndrome are thought to be multifactorial[48]. Defective fibrillin protein caused by mutations in the FBN1 gene causes structural and functional perturbation of connective tissues may predispose individuals to SCAD[49]. However, no specific connective tissue disorders or extracoronary vascular phenotypes in patients with SCAD have been observed[48]. A recent study[50] highlighted the role of extracellular matrix dysfunction in SCAD. Specifically, in this large cohort, across all patients with SCAD, rare disruptive variants were found within 10 collagen genes among individuals with SCAD compared with 2506 constrained genes expressed in the coronary artery[50]. Furthermore, patients with SCAD were 1.75-fold more likely to carry disruptive rare variants within fibrillar collagen genes[50]. Other collagen vascular disorders that have been proposed to be associated with SCAD are Alport syndrome and Nail-patella syndrome[51,52].

Thyroid dysfunction could be another possible risk factor for SCAD. In hypothyroidism, the lack and impairment of thyroid hormones might lead to impairments in the structure of the artery wall, making coronary arteries more prone to SCAD[46]. In a previous study, investigators showed that the prevalence of hypothyroidism was significantly higher (26%) in patients with SCAD compared to patients with ACS[53]. In the same study, patients with both SCAD and hypothyroidism had more distal lesions and more tortuous coronary arteries. However, more data is required to support this finding.

Finally, the role of genetics in SCAD is a complex issue. Most recent studies have involved genetics as a predisposing factor in SCAD. SCAD has not been shown to be strongly familial, but it is more likely that cases within families are scattered and independent of specific genes. However, a recent study[54] highlighted the PHACTR1/EDN1 gene as directly associated with SCAD and other cardiovascular conditions such as coronary artery disease. The authors showed that patients who carried the rs9349379-A allele had an increased risk of FMD and SCAD[54]. This association requires further investigation.

## CLINICAL SYMPTOMS

There is a wide spectrum of clinical presentation and severity of SCAD. Patients with SCAD usually present at the emergency department with chest discomfort as the most common symptom[55], chest pain, and rapid heartbeat or fluttery. Less frequent symptoms include pain to the arms or neck, nausea or vomiting, unusual or extreme tiredness, shortness of breath and back pain[16]. A percentage between 24% and 87% of patients with SCAD demonstrate STEMI alterations in the ECG and elevation of cardiac enzymes[7,13,56,57]. A smaller percentage of patients, present complications such as ventricular arrhythmias (3% to 10%), cardiogenic shock (< 3%) and sudden cardiac death (< 1%)[11,13,30]. Another characteristic of SCAD is reduced left ventricular ejection fraction (EF) (< 50%), observed in almost 44%–49% of patients. However, there are usually significant improvements in the EF after treatment of

the arterial dissection[13,58]. In Canada, patients with SCAD expressed their chest pain either as radiation to the arm (approximately 50%) and/or neck (approximately 22%), dyspnea (approximately 19%) and pain in the back (approximately 12%) or as nausea and vomiting (approximately 23%) and hyperhidrosis (approximately 21%)[55]. However, in a minority of patients, chest pain could also be atypical[55].

## DIAGNOSTIC METHODS AND ANGIOGRAPHIC CLASSIFICATION

Accuracy and early diagnosis are the most important factors for the management of SCAD. Coronary angiography is the gold standard and the first-line imaging technique for patients presenting with ACS. Administration of intracoronary nitrates, intracoronary imaging when safe and available, and/or follow-up noninvasive or invasive coronary imaging may be helpful in order to distinguish SCAD from other etiologies of ACS[18].

The main limitation of coronary angiography is that the 2-dimensional luminogram does not allow us to display the arterial wall[24,26]. As a result, further imaging techniques are required in order to set a definitive diagnosis. Intracoronary imaging, including OCT and intravascular ultrasound (IVUS) (Figure 1), is the supplementary method that improves SCAD diagnosis and has the possibility to display the arterial wall layers compared to coronary angiography[24,26]. Important disadvantages are that it is not widely available, it is often associated with additional risks and higher costs and, it requires instrumentation of the coronary artery, a situation which in SCAD could pose a challenge. Coronary computed tomography angiography has lower spatial resolution compared with conventional angiography and presents challenges in the evaluation of lumens and walls of small coronary arteries [9].

Optical coherence tomography, with an axial resolution of 15 μm, is a supplementary intracoronary imaging method for the diagnosis of SCAD that provides higher spatial resolution[40]. Despite this important advantage, OCT requires blood clearance using a high-pressure contrast injection, a situation that could lead to a further extension of the dissection, and particularly of the false lumen[59]. Nevertheless, the reduction of depth penetration, which is by definition limited in OCT, could lead to safe and accurate diagnosis[6,60]. OCT could also provide specialists with very significant information regarding the true lumen, characteristics related to the false lumen such as the type, size, and the point of extension, as well as its relation with side-branches[60]. In order to locate the characteristic crescentic shape of the false lumen, meticulous image analysis and evaluation are necessary. The practical usefulness of OCT in SCAD patients requiring coronary revascularization is to assure us, before any intervention, the location of the guidewire in the right lumen; thus, avoiding stenting of the false lumen that could cause hazardous complications[61,62].

IVUS, with an axial resolution of 150 μm, is also a supplementary method in SCAD diagnosis, and is able to differentiate atherosclerotic plaques from SCAD[27,59,63,64]. This method clearly illustrates and differentiates the two lumens and can show the severity of false lumen thrombosis. This technique readily depicts the true and the false coronary lumens and is also able to demonstrate the extent of false lumen thrombosis. IVUS presents great advantages over OCT. The major advantages are that pressurized contrast injection to clear blood from the lumen is not required and depth penetration is superior, enabling full imaging through the thrombus of the vessel wall up to the exterior elastic lamina [59]. The primary drawback of IVUS is its poor spatial resolution, making it difficult to identify small structures related to the disease, such as the intimal-medial membrane and localized fenestrations linking the two lumens[65,66].

MRI is another new diagnostic method for patients with SCAD. Specifically, MRI can diagnose SCAD when its underlying diagnosis cannot be initially recognized on angiography[67]. The characteristic findings of MRI in patients with SCAD are (1) late gadolinium enhancement which could be transmural, affected by myocardium, subendocardial, and with patchy enhancement; (2) microvascular obstruction; and (3) IMH[67,68]. Cardiac magnetic resonance (CMR) imaging demonstrating delayed gadolinium enhancement in an area with suspected dissection could help in the confirmation of SCAD. However, normal CMR imaging may not exclude SCAD. A substantial minority of patients with angiographically-confirmed SCAD do not have CMR evidence of infarction[18,68].

An important key-point in the differential diagnosis of SCAD would be the discrimination between non-atherosclerotic SCAD and coronary artery dissection caused by atheromatic plaque rupture in patients with atherosclerosis or catheter-induced iatrogenic dissections. The absence of atheroma or calcification in patients with non-atherosclerotic SCAD causes more fragile arterial walls and it is difficult to limit the expansion of the dissection[24]. Therefore, patients in this category often present more extensive dissections, while non-affected coronary artery segments appear smooth on angiography[24]. A proposed diagnostic algorithm from our Institution is demonstrated in Figure 2.

The classification of SCAD is based on angiographic imaging techniques. There are 3 widely approved types of SCAD[7] (Figure 3): Type 1 describes the pathognomonic appearance of arterial wall contrast staining with multiple radiolucent lumens with or without dye hang-up or slow contrast clearing[30]. Type 2 describes diffuse smooth stenoses of varying severity and length (typically > 20

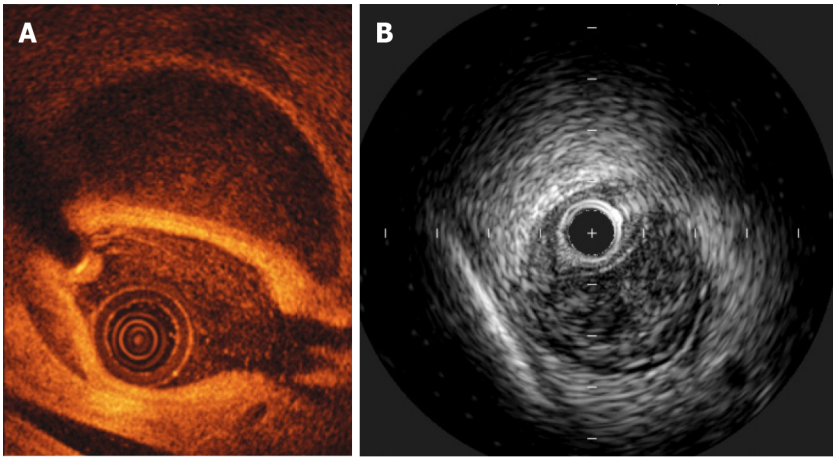


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**Figure 1 Intravascular imaging techniques in spontaneous coronary artery dissection.** A: Optical coherence tomography; B: Intravascular ultrasound.

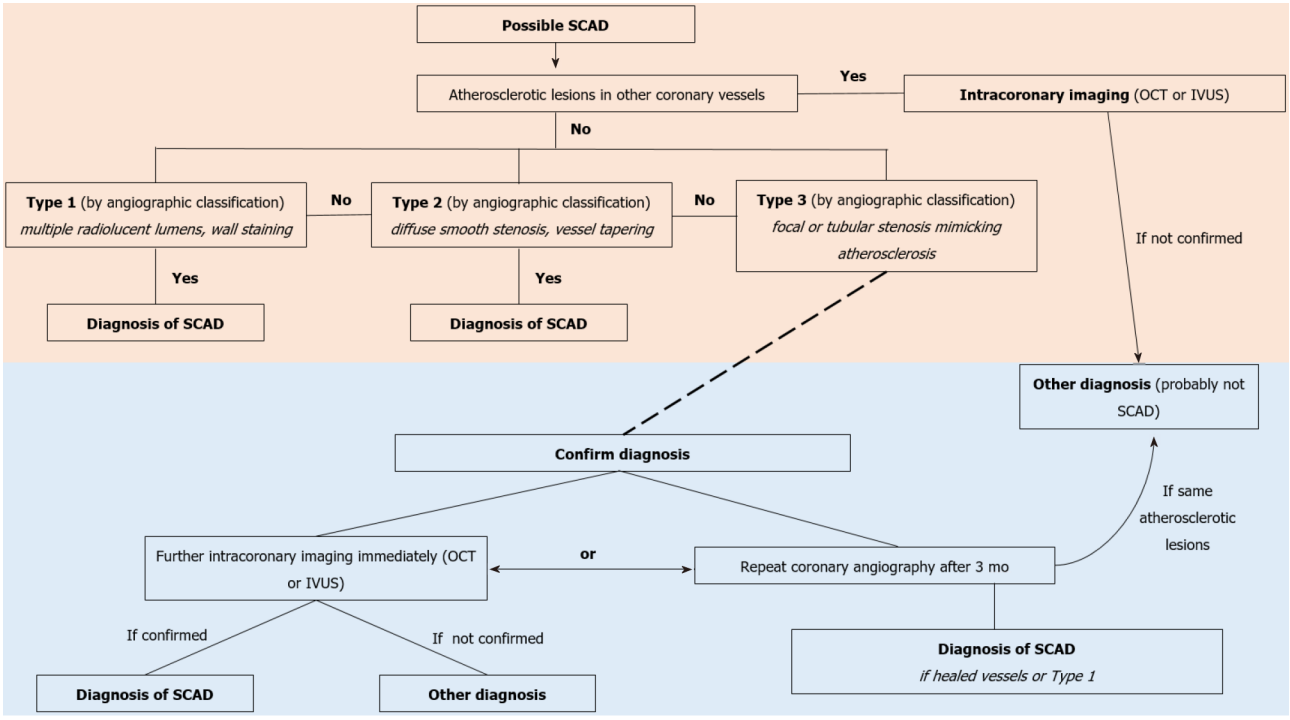


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**Figure 2 Flowchart diagram for the diagnosis of spontaneous coronary artery dissection.** OCT: Optical coherence tomography; IVUS: Intravascular ultrasound; SCAD: Spontaneous coronary artery dissection.

mm). It usually has abrupt changes in the arterial caliber from the normal diameter to diffuse smooth narrowing. The diffuse narrowing is bordered by normal artery segments proximally and distally to the IMH in type-2A variant, while it extends to the apical tip of the artery in type-2B variant[24]. Type 3 describes a focal or tubular (typically < 20 mm) stenosis mimicking atherosclerosis requiring supplementary techniques to diagnose IMH or double-lumen, such as OCT and IVUS[24].

The most common angiographic type of SCAD is type 2, observed in approximately 67% of dissected arteries[7,11,40,69]. The left anterior descending artery is the most frequently affected (32%-46%)[7,11,40,69].

## THERAPEUTIC STRATEGIES

One of the most controversary issues of modern cardiology is the management strategy of SCAD. There

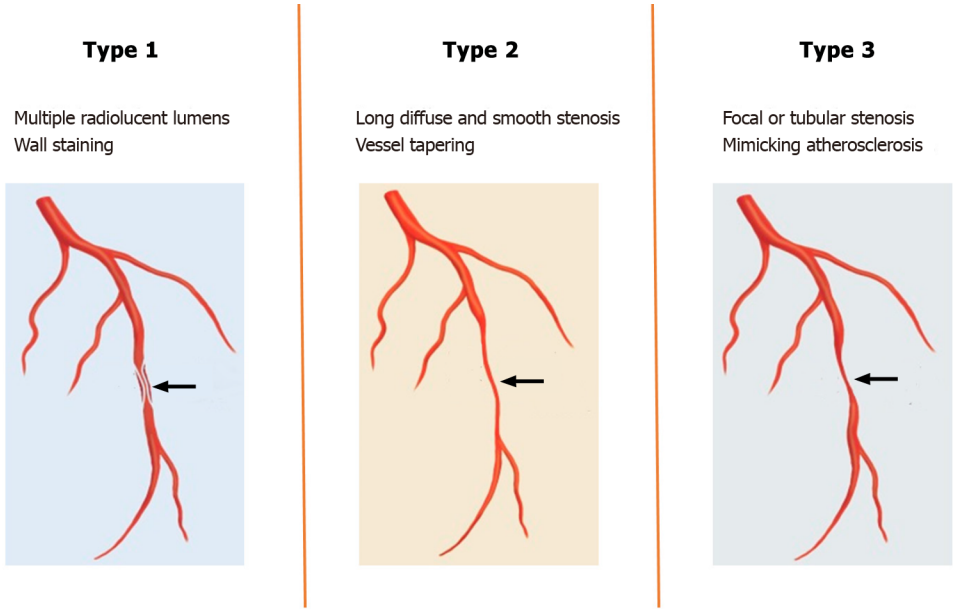


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**Figure 3 Types of spontaneous coronary artery dissection based on angiographic imaging techniques.**

are no randomized controlled trials to compare the effect of medical therapies and revascularization strategies in these patients in order to contribute to the determination of the optimal management of SCAD. It also remains unclear whether guideline-indicated medical therapies administered for ACS would be beneficial in SCAD[70]. Therefore, management strategies are usually based on expert opinions. There is a special category of patients with SCAD, often presenting with cardiogenic shock. Pregnancy-associated SCAD is associated with dissection of more prominent epicardial vessels, leading to extensive myocardial injury and life-threatening arrhythmias[21]. As a result, these patients typically present with ACS complicated by acute heart failure or cardiogenic shock[21]. The therapeutic approach in these patients may include immediate hemodynamic support with mechanical circulatory support, extracorporeal membrane oxygenation, intra-aortic balloon pump (IABP), and left ventricular assist device (LVAD), in combination with revascularization or even cardiac transplantation[71,72]. Case reports have demonstrated beneficial effects of these therapeutic approaches in pregnant women with SCAD and cardiogenic shock[73].

### *Conservative management*

The aim of conservative management in the acute phase of SCAD is to restore or preserve myocardial perfusion and cardiac function. Medical therapy includes beta-blockers and aspirin. The beneficial effect of beta-blockers in reducing shear stress of the coronary artery walls is associated with lower risk of recurrence, especially in patients with significant impairment of left ventricular systolic function[1,40]. Other medical therapies related to the reduction of arterial pressure and protection of the myocardium, such as angiotensin converting enzyme, angiotensin receptor blocker or mineralocorticoid receptor antagonist, are also indicated in SCAD[74,75].

The use of antiplatelets and anticoagulants, as well as the duration of treatment, remain controversial in SCAD. Patients who undergo stenting have an indication to receive dual antiplatelet therapy for 12 mo and lifelong monotherapy (usually aspirin) while acute dual antiplatelet therapy (usually with aspirin and clopidogrel) is suggested for patients managed conservatively[34,40,74,75]. The indication for acute administration of anticoagulants is only during revascularization while the indication for chronic use is in the case of left ventricular thrombus or thromboembolism[65]. However, all the above approaches remain questionable and further evidence is required.

The role of lipid-lower therapies is unclear and controversial. Statins could be recommended for routinely use after MI and in patients with pre-existing dyslipidemia[40,76]. SCAD is characterized by a general lack of atherosclerosis, and, therefore, statins may not be effective in patients with a normal lipidemic profile.

Thrombolysis is contraindicated in the acute management of SCAD as it might extend dissection and cause coronary rupture, leading to cardiac tamponade[77,78]. Adverse outcomes related to thrombolytics, including extension of dissection or hematoma, have been reported in SCAD[79].

### *Revascularization*

Percutaneous coronary intervention is associated with poor success rates (50%-70%) due to the

increased risk of potential coronary complications including iatrogenic catheter-induced dissections, extension of dissections, and failure to enter into the true lumen[61,80]. Furthermore, there is an increased risk of proximal and/or distal false lumen propagation during stent deployment[44,81] and major side branch restriction or occlusion by propagation of the hematoma[59]. Secondary iatrogenic dissection is a major risk for patients undergoing invasive treatment. Increased risk of secondary iatrogenic dissections during coronary angiography (2%), non-SCAD angiography (0.2%) and PCI (14.3%) has been reported in SCAD patients[23]. Another study also demonstrated an increased percentage of secondary dissections related to catheterization maneuvers in patients with SCAD (5%) [12]. Taking all these factors into consideration, meticulous co-axial catheter technique and avoidance of aggressive catheterization maneuvers are suggested for patients with an indication for revascularization, while a conservative approach would be the preferred strategy in clinically stable SCAD patients with no evidence of ongoing ischemia[11,13]. Moreover, in SCAD patients, catheterization through femoral access would be preferable than radial access. Data have shown a 3-fold higher risk for catheter-induced iatrogenic dissection in patients with SCAD undergoing coronary angiography by radial access compared to femoral access[11,23].

There are specific indications for revascularization. Patients with hemodynamic instability, ongoing or recurrent ischemia, ventricular arrhythmias, or left main dissection should be considered for PCI[1, 9]. A necessary condition for PCI is the suitable anatomy of the coronary arteries. Meticulous catheter wire and guide-wire manipulation, avoidance of deep catheter engagement, noncoaxial positioning of the catheter tip, catheter dampening, and/or strong contrast injections are measures that should be implemented in order to minimize complications[13,82]. All medical procedures should be undertaken with extreme attention in order to prevent catheter-induced dissection. Less conventional interventional approaches include minimal plain old balloon angioplasty to restore flow[83], longer stents to lower the possibility of further extension of the hematoma[59], and other similar techniques[84-87].

Coronary artery by-pass grafting (CABG) could be considered for patients with left main dissections with ongoing ischemia, extensive dissections, in cases where PCI failed and in patients who are not anatomically suitable for PCI[1,59]. CABG as a treatment strategy for SCAD is usually associated with promising in-hospital outcomes[12]. However, there are no clinical trials to prove the beneficial effect of CABG compared to PCI. In contrast, retrospective studies have shown high rates of graft failure at follow-up[12]. There are only case reports suggesting CABG over PCI in peripartum SCAD in order to avoid complications or sudden cardiac death due to extension of the dissection and aneurysm formation [88]. Although CABG has not been shown to prevent recurrent SCAD[12], it still remains an important therapeutic strategy, providing coronary blood flow and myocardial perfusion in critically ill patients. Despite concern for inadequacy of distal targets in diffusely dissected vessels, successful graft anastomoses are usually achieved in every primary vessel and almost all secondary vessels in all patients treated with CABG during index hospitalization, including patients initially managed conservatively or with PCI[12]. A potential risk of CABG is the fact that dissected coronary artery tissues are profoundly fragile, unlikely to hold suture, and prone to anastomotic complications[18]. A medical history of connective tissue disorders may increase the risk. Another possible complication of CABG in patients with SCAD is the high rates of bypass conduit failure due to the fact that healing of the native coronary arteries results in increasing competitive flow[12,18]. There is still not enough evidence on whether arterial or venous grafting demonstrates better outcomes in patients with SCAD. Thus, the use of reliable and immediately high-flow venous conduits could be suggested, particularly in hemodynamically unstable patients with large territories of myocardium on ongoing ischemia[18].

A proposed management algorithm for SCAD is shown in Figure 4.

## PROGNOSIS AND FOLLOW-UP

The prognosis of SCAD is usually good and patients surviving SCAD demonstrate low long-term mortality[11,12,13]. Specifically, 49.7% to 89.7% of patients with SCAD received medical therapy as initial treatment, and 2.6% to 8.5% of conservatively treated patients eventually required revascularization during the index hospitalization[11,12,13]. Revascularization with PCI is the initial treatment for SCAD in 16.7% to 47.1% of patients[11,12,13]. Reported PCI success rates vary from 36.4% to 72.5%, which is significantly lower than the success rates in control subjects with atherosclerotic ACS[11,12,13]. Emergency CABG is required in 2.2% to 7.4% of patients who initially received medical therapy or PCI. An initial CABG revascularization approach was used in 0.6% to 3.7%, and initial success was high in this small group of patients, ranging from 87.5% to 100%[11,12,13]. During a follow-up of 2 to 3 years, major adverse cardiac events related to recurrent SCAD were reported in 10% to 30% of cases[3,11,29, 40]. At longer-term follow-up, major adverse cardiac events predominantly related to recurrent SCAD were reported in 15% to 37% at 5 to 7 years, while the estimated rate of major adverse cardiac events was approximately 50% at 10 years[3,11-13,29]. Conservative therapeutic strategies including medical therapy have shown excellent long-term prognosis at 6 years with event-free survival rates between 88% and 94%[89]. Another case series in United States reported a 10-year survival of 92%[29]. Similarly, a case series in Italy reported a 94.4% 6-year survival[13] while, in Canada, mortality was estimated at

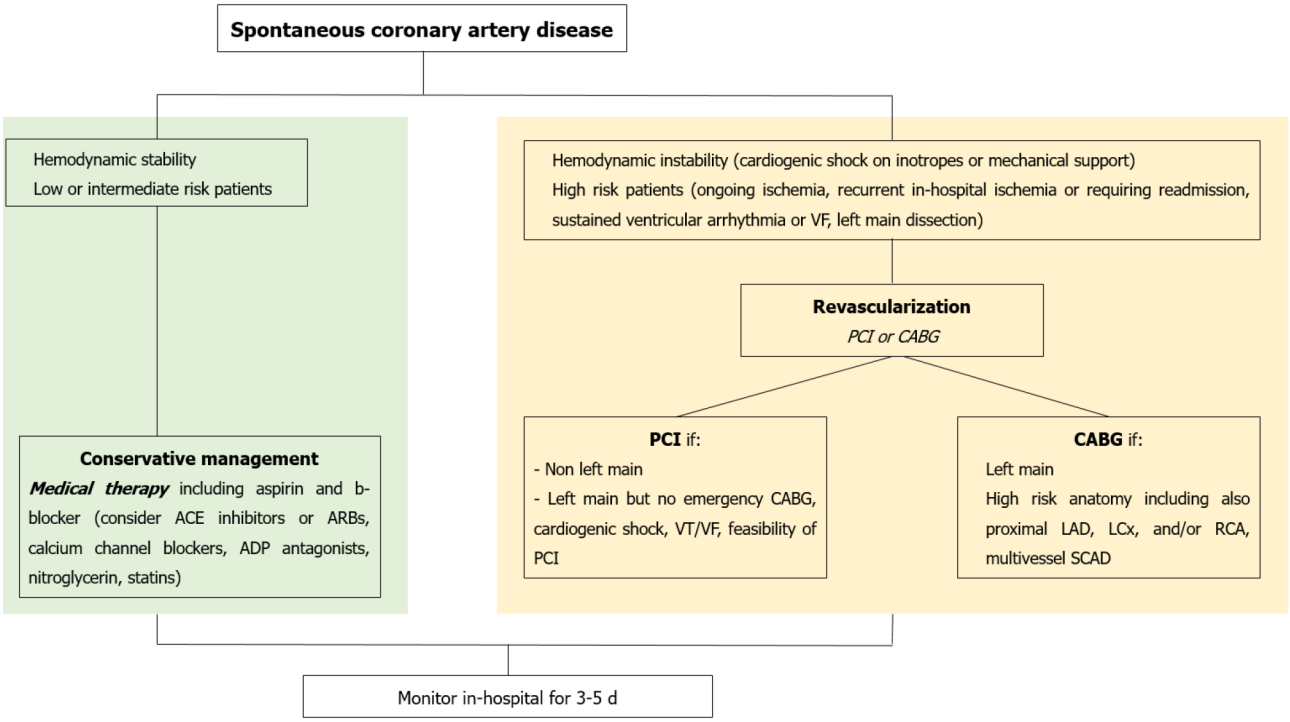


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**Figure 4 Proposed management algorithm for spontaneous coronary artery dissection.** VF: Ventricular fibrillation; ACE: Angiotensin converting enzyme; ADP: Adenosine diphosphate; CABG: Coronary artery by-pass grafting; VT: Ventricular tachycardia; PCI: Percutaneous coronary intervention; LAD: Left anterior descending artery; LCx: Left circumflex coronary; RCA: Right coronary artery; SCAD: Spontaneous coronary artery dissection.

1.2% in 3.1 years[40]. Studies with a small number of SCAD patients, such as the Swiss series and the Japanese series, either did not demonstrate deaths in 63 patients at a median 4.5-year follow-up[56] or demonstrated a single death among 63 patients who were followed up for 34 mo[3], respectively. However, recurrent dissections and high rates of target vessel failure are significant factors that caused major adverse cardiac events ranging from 14.6% to 47.4% in SCAD patients who underwent PCI in the above case series[3,13,29,40]. SCAD recurrence was 17% in United States patients within a 4-year follow-up, approximately 29% within 10 years, and the period between the two events was at 2.8 years[29]. The corresponding percentage in the Canadian case series was 10.4% within 3.1 years, while the percentage of a new MI event was approximately 17%[40]. The Japanese series study showed recurrent SCAD of 11% after 1 mo from the first episode, during their 34-mo follow-up[3]. In the Swiss series study, 3 patients had recurrent SCAD out of 63 patients followed-up for a median of 4.5 years[56]. Finally, the Italian series study reported a 4.7% recurrence rate over a median 22-mo follow-up[13].

Follow-up of SCAD patients should be performed every year with imaging methods including simple techniques such as echocardiography and cardiac magnetic resonance imaging, more complex techniques such as computed tomography-peripheral angiography or magnetic resonance-angiography, and invasive techniques such as coronary angiography[59]. Coronary computed tomography angiography was shown to be a valuable and useful method, without complications, for noninvasive follow-up of patients with SCAD, especially in those with large-caliber coronary arteries[57,90,91]. A significant limitation of coronary computed tomography angiography is the poor visualization of SCAD lesions in distal coronary arteries or side branches, or of vessel caliber < 2.5 mm[11,92]. For all patients, either treated conservatively or those who underwent PCI, a follow-up angiography in the catheter laboratory is suggested 6 mo after the event, in cases where coronary computed tomography angiography is not feasible or misdiagnosing. Repeat angiograms can be performed by the femoral or radial approach during a short hospital stay or on an ambulatory basis[93]. Patients should also have outpatient appointments at the referring hospital or with cardiologists in private practice twice within the first year of the event; typically, 1 to 3 mo and 12 mo after the event. Thereafter the appointments depend on the clinical status of each patient[93]. Other non-invasive follow-up techniques including cardiopulmonary exercise stress test and echocardiography should be conducted every year. In pregnancy, pregnant women with a medical history of SCAD should be referred to specialized medical centers for assessment, counseling for the potential increased risk of dissection and complications during pregnancy, and follow-up by a multidisciplinary team that includes maternal-fetal medicine specialists, cardiologists with experience managing SCAD, and obstetric anesthesiologists[83]. In patients with systemic arteriopathy, an extracoronary dissection or an aneurysm, subsequent use of alternative imaging methods that do not expose the patient to ionizing radiation such as magnetic

resonance angiography and duplex ultrasonography should be considered[94]. Major adverse cardiac events should be registered in all patients with SCAD at follow-up, especially in the first 5 years.

## EXERCISE AND LIFESTYLE AFTER SCAD

In most SCAD patients, especially those with recurrence or noncoronary aneurysms or dissections, it is suggested thay they avoid extreme endurance training, exercise until exhaustion, elite competitive sports, or vigorous exertion in extremes of ambient temperature. Additionally, patients should avoid lifting or carrying heavy objects that require straining or prolonged Valsalva maneuvers[18]. The onset of SCAD symptoms has been correlated with physical activity in up to 32% of patients after SCAD[95]. After the onset of chest pain, patients should be immediately evaluated according to proposed algorithms in previous articles[18].

High levels of psychological distress including depression, anxiety, and post-traumatic stress disorder are associated with post-SCAD patients, especially women. Psychological support is always recommended in patients with cardiovascular diseases[96].

## CURRENT DEVELOPMENTS AND FUTURE PERSPECTIVES

The current progress in early recognition and appropriate therapeutic management of SCAD has improved the understanding of the pathophysiology background of the disease, its association with potential risk factors and the role of genetics. Diagnostic management includes high-resolution diagnostic methods such as OCT, IVUS, cardiac MRI and duplex ultrasonography. Progress has also been noted in the therapeutic strategies of the disease. Life-saving technologies, especially in patients with hemodynamic instability, including mechanical circulatory support systems, extracorporeal membrane oxygenation, IABP, and LVADs, as well as new revascularization techniques and progress in cardiac transplantation have increased survival rates and reduced complications in these patients.

However, data remain retrospective, observational, and often based on case reports. Collaborative evaluations across medical centers are further required. National registries and continuous follow-up programs at 1, 3, 6 and 12 mo, with or without intravascular imaging, would provide more evidence for the disease, leading thus, to more comprehensive points of view regarding accurate diagnosis of SCAD among AMI and chest pain, appropriate indications and optimal techniques for revascularization, optimization of medical therapy, individualization of risk factors for recurrent SCAD and better development of genetic model systems for better understanding of genetic variations of SCAD. Invasive approaches with the use of bioresorbable vascular scaffolds should be encouraged in proximal/middle vessel lesions, occurring in larger vessels (≥ 3.0 mm vessel diameter) and in cases where patients are still symptomatic or hemodynamically unstable[97,98]. Finally, the establishment of new accurate scores for the diagnosis and therapeutic management of SCAD is mandatory.

## CONCLUSION

SCAD is a rare cardiovascular disease which mostly affect women (approximately 90%), but there are limited data regarding diagnosis and treatment. The increased awareness of SCAD during the last decade has improved our knowledge regarding the potential mechanisms of the disease. Alertness and education are the most important alliances of the medical community in the early and accurate diagnosis of SCAD, especially among women, and its treatment strategies. Coronary angiography is the gold standard treatment method in unstable patients with symptoms of acute ischemia. OCT and IVUS are supplementary intracoronary imaging techniques in the diagnosis of SCAD, and they should be performed before each intervention in order to increase safety and reduce secondary iatrogenic dissections related to stenting. Further randomized controlled trials in medical centers, investigating different diagnostic methods and different therapeutic approaches, are required.

## FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

# Role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cryoballoon ablation outcomes for paroxysmal atrial fibrillation

Ibragim Al-Seykal, Abhishek Bose, Parag A Chevli, Zeba Hashmath, Nitish Sharma, Ajay K Mishra, Douglas Laidlaw

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## Abstract

### *BACKGROUND*

Cryoballoon ablation (CBA) is recommended for patients with paroxysmal atrial fibrillation (AF) refractory to antiarrhythmic drugs. However, only 80% of patients benefit from initial CBA. There is growing evidence that pretreatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) decreases the recurrence of AF postablation, particularly in nonparoxysmal AF undergoing radiofrequency ablation. The role of ACEIs and ARBs in patients with paroxysmal AF in CBA remains unknown. We decided to investigate the role of ACEIs and ARBs in preventing the recurrence of atrial arrhythmia (AA) following CBA for paroxysmal AF.

### *AIM*

To investigate the role of ACEIs and ARBs in preventing recurrence of AA following CBA for paroxysmal AF.

### *METHODS*

We followed 103 patients (age 60.6 ± 9.1 years, 29% women) with paroxysmal AF undergoing CBA 1-year post procedure. Recurrence was assessed by documented

AA on electrocardiogram or any form of long-term cardiac rhythm monitoring. A multivariable Cox proportional hazard model was used to assess if ACEI or ARB treatment predicted the risk of AA recurrence.

***RESULTS***

After a 1-year follow-up, 19 (18.4%) participants developed recurrence of AA. Use of ACEI or ARB therapy was noted in the study population. Patients on ACEI/ARB had a greater prevalence of hypertension and coronary artery disease. On a multivariate model adjusted for baseline demographics and risk factors for AF, ACEI or ARB therapy did not prevent recurrence of AA following CBA ($P$ = 0.72). Similarly, on Kaplan–Meier analysis pretreatment with ACEI/ARB did not predict the time to first recurrence of AA ($P$ = 0.2173).

***CONCLUSION***

In our study population, preablation treatment with an ACEI or ARB had no influence on the recurrence of AA following CBA for paroxysmal AF.

**Key Words:** Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Paroxysmal atrial fibrillation; Cryoballoon ablation; Outcome



**Core tip:** We investigated the role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in preventing recurrence of atrial arrhythmias following cryoballoon ablation (CBA) for paroxysmal atrial fibrillation (AF). Outcomes of 103 patients were evaluated in a retrospective chart review. Preablation treatment with an ACEI or ARB had no influence on recurrence of AA following CBA for paroxysmal AF. To our knowledge, this study is the first of its kind to examine the effect of ACEI/ARB use in this exclusive subset of patients.

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## INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia that represents an evolving, global epidemic[1]. It is estimated that the number of Americans afflicted by AF will increase from the current 2.3 million to more than 10 million by 2050[2]. Due to a substantial increase in incidence and prevalence of AF over the past few decades, it presents a significant economic burden on the health care system[3]. In 2014, in the United States alone, an estimated 599790 emergency department visits, 453060 hospitalizations, and 21712 deaths were associated with AF as a primary medical diagnosis. Furthermore, the mean cost per hospitalization for patients with a primary diagnosis of AF was $88194[4].

Even though cryoballoon ablation (CBA) is beneficial in patients with paroxysmal AF refractory to antiarrhythmic drugs, only 80% of patients benefit from initial CBA[5-8]. Myocardial fibrosis is a known risk factor for the development of AF and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are known agents that prevent remodeling. There is growing evidence that pretreatment with ACEIs and ARBs decreases the recurrence of AF postablation, particularly in nonparoxysmal AF undergoing radiofrequency ablation (RFA) [9]. The role of ACEIs and ARBs in patients with paroxysmal AF in CBA remains unknown. In this study, we aimed to investigate the role of ACEIs and ARBs in preventing recurrence of atrial arrhythmia (AA) following CBA for paroxysmal AF.

## MATERIALS AND METHODS

### *Study design and definitions*

We performed a single-center, retrospective, cross-sectional study in a community-based tertiary care center in Worcester, MA, USA. Paroxysmal AF was defined as nonsustained episodes of AF converting

to sinus rhythm in < 7 d. Patients were required to be on an ACEI or ARB for a minimum duration of 4 wk. Institutional review board approval was obtained before initiation of the study.

### Inclusion and exclusion criteria

To be included in this study, participants had to be aged ≥ 18 years and have had CBA as a first or repeat procedure for paroxysmal AF between January 2015 and April 2018. We excluded all patients with a diagnosis of permanent and persistent AF. Following inclusion data on baseline demographics, concomitant comorbidities, clinical, laboratory, echocardiographic, pharmacological and ablation procedural details and outcome details were obtained by trained physicians from chart review.

### Cryoablation procedure

All CBA were conducted under general anesthesia. Two sheaths (7 and 9 Fr) were placed in the left femoral vein following ultrasound-guided vascular access. With the fluoroscopic guidance, an intracardiac echocardiography (ICE) catheter was advanced into the right atrium and a decapolar mapping catheter was positioned within the coronary sinus. A trans-septal sheath was placed through the right femoral vein approach. Heparin was administered intravenously for an activated clotting time > 300 s to prevent intraprocedural thromboembolic events. Trans-septal access to the left atrium was obtained under fluoroscopic and ICE guidance. The trans-septal sheath was exchanged for a 12 Fr Flexcath sheath (Medtronic, Minneapolis, MN, USA) which was then utilized to advance a 28-mm Arctic Front Advance Cryoballoon ablation catheter (Medtronic) with the Achieve spiral mapping catheter into the left atrium. An electroanatomic map of the left atrium and all pulmonary veins was performed utilizing 3-dimentional mapping software (Abbott Cardiovascular, Santa Clara, CA, USA), guided by a three-dimensional computed tomography recreation of the left atrium. Each of the pulmonary veins were then isolated using CBA. During the right-sided pulmonary vein ablation, the decapolar catheter was withdrawn to the superior vena cava to pace the diaphragm and allow for monitoring of phrenic nerve injury. For pulmonary veins with incomplete isolation following CBA, local RFA was performed as needed to provide complete isolation. All pulmonary veins have demonstrated a bidirectional conduction block and a postablation voltage map was created using the mapping software.

### Follow up for ablation success

The patients with paroxysmal AF undergoing CBA were followed for 1 year postprocedure for any development of AA. The recurrence of AA was assessed through a medical records review by documented self-reported patient symptoms, supplemented by an electrocardiogram or any form of documented long-term rhythm monitoring such as a cardiac event or a Holter monitor. A 3-mo blanking period was used postablation to allow for recurrence of AF after the initial procedure, with the exception for symptomatic patients with early recurrence that required electrical cardioversion or repeat ablation.

### Statistical analysis

We reported continuous variables as mean with standard deviation and categorical variables as frequency and percentage. A multivariable Cox proportional hazard model was used to assess if ACEI or ARB treatment predicted the risk of AA recurrence. For the multivariate analysis, we utilized two models. In the first model, analysis was adjusted for nonmodifiable variables including age and gender. In the second model, analysis was adjusted for both nonmodifiable (Model 1) and modifiable variables including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease (CAD), heart failure (HF), chronic kidney disease stage ≥ 3, and at least moderate degree of any valvular heart disease. The $\chi^2$ test was used to analyze the significance of the categorical variables and Student's *t*-test was used to analyze the significance of continuous variables. To look for the association between ACEI/ARB use and recurrence of AA, we used the multivariable Cox- proportional analysis and calculated hazard ratio (HR) and 95% confidence interval (CI). We used the Kaplan–Meier method to obtain survival curves and a log-rank test for their comparison. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all these statistical analyses. $P < 0.05$ was considered to be statistically significant.

## RESULTS

Between January 2015 and April 2018, 103 patients undergoing CBA as a first or repeat procedure for paroxysmal AF were included in this study. They were divided into two groups based on the use of ACEIs/ARBs at the time of CBA. Their baseline characteristics are presented in Table 1. Out of the 103 patients, 42 were receiving ACEIs/ARBs at the time of CBA. The mean age was similar in both groups (61.7 ± 8.6 years in the ACEI/ARB group *vs* 59.9 ± 9.5 years in the other group). Patients in the ACEI/ARB group were more likely to be male (78.6% *vs* 65.6%) and have hypertension (86% *vs* 54.1%) and CAD (26.2% *vs* 9.8%). Out of the 42 patients, 21 (58%) were taking ACEIs and 15 (42%) were taking ARBs. In the ACEI group, all patients were taking lisinopril. In the ARB group, 87% of patients were taking losartan. The mean dose for lisinopril was 16 mg orally daily and the median dose was 10 mg

**Table 1 Baseline characteristics of study participants**

| Characteristics | No ACEI / ARB | ACEI / ARB | *P* value |
|---|---|---|---|
| mean ± SD or *n* (%) | *n* = 61 | *n* = 42 | |
| Age (yr) | 59.9 ± 9.5 | 61.7 ± 8.6 | 0.32 |
| Male | 40 (65.6%) | 33 (78.6%) | 0.15 |
| Baseline heart rate | 70 ± 15.7 | 63 ± 17.8 | 0.06 |
| Body mass index (kg/m$^2$) | 30.9 ± 76.6 | 32.3 ± 6.9 | 0.33 |
| Coronary artery disease | 6 (9.8%) | 11 (26.2%) | 0.028 |
| Congestive heart failure | 6 (9.8%) | 9 (21.4%) | 0.10 |
| Diabetes mellitus | 9 (14.8%) | 12 (28.6%) | 0.09 |
| Hypertension | 33 (54.1%) | 36 (85.7%) | < 0.001 |
| Valvular heart disease | 25 (41.0%) | 14 (33.3%) | 0.43 |
| Hyperlipidemia | 40 (65.6%) | 31 (73.8%) | 0.37 |
| CHA2DS2VASC score | 1.5 ± 1.4 | 2.0 ± 1.3 | 0.08 |
| Recurrence of AA | 9 (14.8%) | 10 (24.4%) | 0.22 |

*P* value as calculated by *t*-test for continuous and $\chi^2$ for categorical variables. SD: Standard deviation; AA: Atrial arrhythmia; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

orally daily. For patients taking losartan, the mean and median doses were 57 and 50 mg orally daily, respectively.

At 1-year follow-up, 19 (8.4%) patients developed recurrence of AA (Figure 1). The role of ACEIs and ARBs in preventing the recurrence of AA following CBA for paroxysmal AF was assessed using a multivariable Cox proportional hazard model (Table 2). In the initial model adjusted for age and sex, ACEI/ARB use did not have a significant impact on AA recurrence after CBA for paroxysmal AF (HR 1.78, 95%CI 0.72–4.42, *P* = 0.66). In a second model adjusted for CAD, congestive HF, diabetes mellitus, hypertension, and valvular heart disease, ACEI/ARB use still did not have a significant impact on AA recurrence after CBA for paroxysmal AF (HR 1.37, 95%CI 0.51–3.7, *P* = 0.72). On Kaplan–Meier analysis, ACEI/ARB use did not predict the time to first recurrence of AA (Figure 2, *P* = 0.2173) in these patients.

## DISCUSSION

In paroxysmal AF patients undergoing CBA, the use of preprocedural ACEI or ARB had no effect on the recurrence of AA at 1 year follow-up. To our knowledge, this study is the first of its kind to examine the effect of ACEI/ARB use in this subset of patients. It is important to note that the ACEI/ARB group of patients that underwent CBA for paroxysmal AF had significantly higher prevalence of hypertension and CAD, which are known to contribute to myocardial fibrosis. Additionally, both hypertension and CAD contributed to increased left ventricular compliance and left atrial filling pressure. Subsequent left atrial enlargement further promotes AA. These comorbidities, however, were adjusted for in multivariate analysis in Model 2 shown above.

The pulmonary veins are the most common substrate for AF initiation[10,11]. Isolated firing of the atrial myocardium can lead to AF initiation initially as an ectopic focus subsequently progressing to a single-circuit re-entry, and eventually to a multiple-circuit re-entry[12,13]. The process correlates with the duration of AF as it progresses from paroxysmal to persistent, and eventually permanent AF5. Myocardial remodeling is one of the key factors in the pathophysiology of AF and is defined as a group of molecular, cellular and interstitial changes that clinically manifest as changes in size, shape and function of the heart resulting from cardiac injury[14]. Additionally, myocardial remodeling can be classified into electrical and structural remodeling. which in turn, can be physiological (adaptive) or pathological[15]. There are several ways in which remodeling could lead to arrhythmia development. The first mechanism involves ion channel changes such as inactivation of sodium ion channels, changes in calcium and potassium ion channels, and alteration in the sodium/calcium exchanger function[5,16-18]. Another mechanism includes changes in the junctional intercellular communication, particularly in protein connexin that is responsible for contact between adjacent cells and electrical coupling[19]. Finally, there is structural cardiac remodeling that involves cell death and fibroblast proliferation that promotes extracellular matrix production, and, eventually, fibrosis[20,21]. Fibrotic lesions impede

**Table 2 Multivariate adjusted Cox-proportional hazard model of atrial arrhythmia recurrence after cryoablation by angiotensin converting enzyme inhibitors/angiotensin receptor blockers**

| Outcome of interest | ACEI/ARB HR (95%CI) | No ACEI/ARB HR (95%CI) | *P* value |
|---|---|---|---|
| Recurrence of AA | | Ref | |
| Model 1[a] | 1.78 (0.72, 4.42) | 1.00 | 0.66 |
| Model 2[b] | 1.37 (0.51, 3.72) | 1.00 | 0.72 |

[a]Model 1 adjusted for age and sex.
[b]Model 2 adjusted for model 1 + coronary artery disease, congestive heart failure, diabetes mellitus, hypertension and valvular heart disease.
AA: Atrial arrhythmia; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; HR: Hazard ratio; CI: Confidence interval.

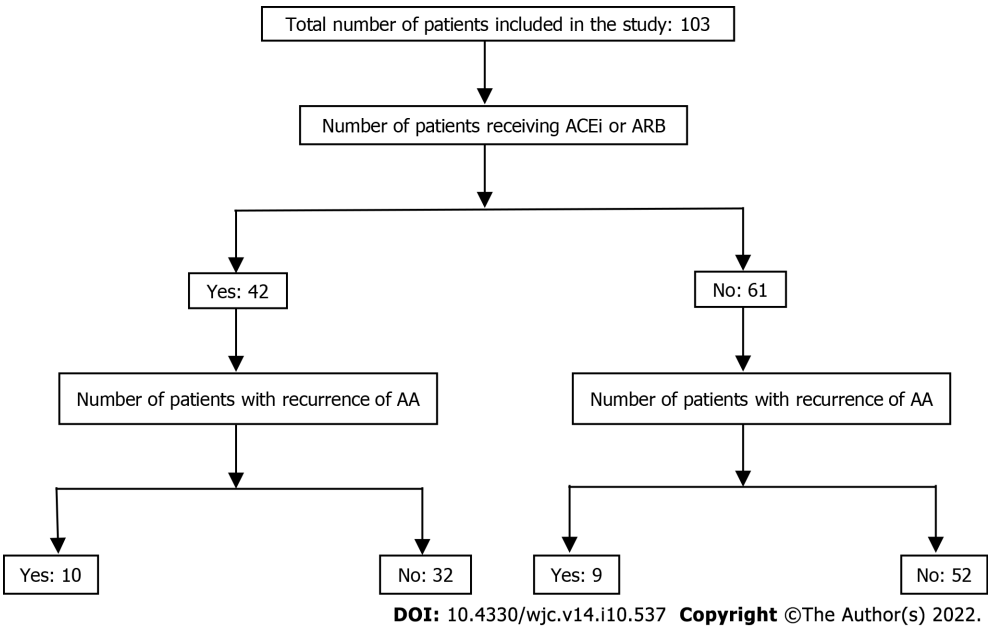

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**Figure 1 STROBE diagram showing flow of patients in the study.** ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; AA: Atrial arrhythmia.

electrical propagation and eventually promote mechanisms for re-entrant arrhythmias[15].

In recent times, there has been a renewed interest in investigating the role of the renin–angiotensin–aldosterone system in AF. There are several ways hypothesized in which ACEIs and ARBs can potentially affect clinical outcomes. These drugs not only have direct effects on the functional remodeling or electrical properties but also indirect effects by controlling hypertension and HF symptoms which are known risk factors for AF[22]. Atrial myocardium is sensitive to increased hemodynamic stressors due to volume and pressure overload from hypertension and HF. These stressors can in turn promote electrical alterations such as decreased resting potential and delayed afterdepolarizations contributing to increased myocardial excitability[23]. Additionally, increased hemodynamic load and myocardial mechanical stretch can activate genetic pathways that rapidly augment the secretion of angiotensin II[24]. Angiotensin II can successively contribute to arrhythmogenicity by promoting an increase net inward calcium current in affected cardiomyocytes and by inducing myocardial hypertrophy and fibrosis[25]. Increased fibrosis of the atrial myocardium is known to be associated with AF[5,20]. G protein-coupled receptor agonists like angiotensin II induce cellular differentiation processes and activation of fibroblasts, and the development of interstitial fibrosis through activation of extracellular signal-regulating kinases (ERKs). These findings were confirmed in a small study by Goette *et al*[26] where patients with AF undergoing cardiac surgery were found to have a significant increase in atrial fibrosis along with an increased expression of ERK1 and ERK2 in atrial interstitial cells.

The use of ACEIs and ARBs has also been shown to be associated with a decreased AF burden in certain population groups. Anné *et al*[27] investigated 196 patients undergoing RFA for atrial flutter and evaluated outcomes associated with the use of an ACEI or ARB. Predictably, more than half of these patients eventually developed AF, but it was found that the use of an ACEI/ARB was associated with reduced incidence of AF after atrial flutter ablation ($P$ = 0.04)[27]. Furthermore, the use of ARBs was

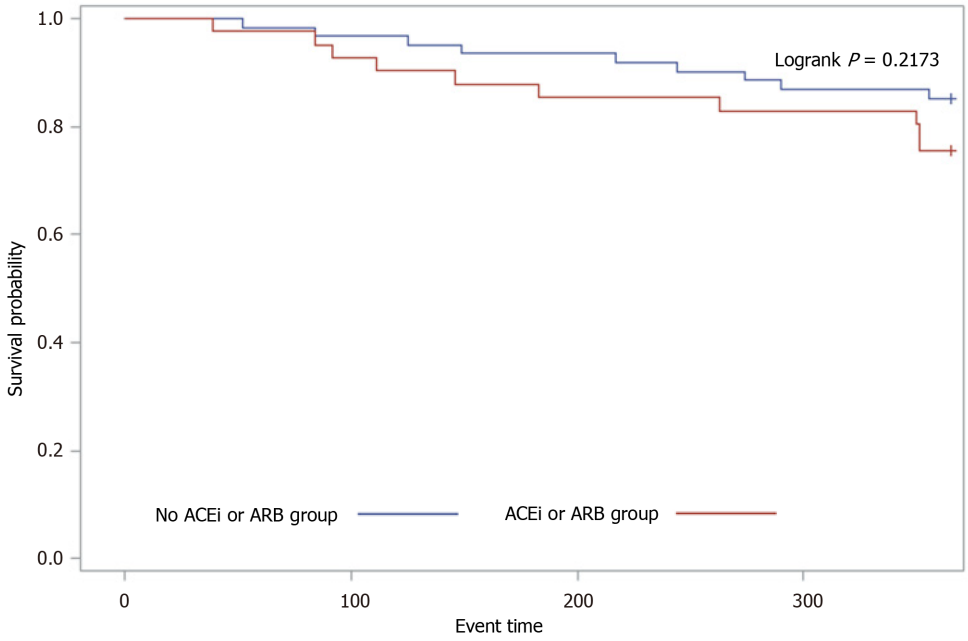


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**Figure 2 One-year Kaplan–Meier Survival curve of atrial arrythmia recurrence after cryoablation by angiotensin-converting enzyme inhibitors / angiotensin receptor blockers use.** AA: Atrial arrhythmia; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

evaluated in conjunction with antiarrhythmic medications and showed better outcomes in comparison to antiarrhythmics alone. In a prospective randomized trial by Madrid *et al*[28], 159 patients were randomized to either amiodarone or amiodarone plus irbesartan to evaluate the role of ACEI in maintaining sinus rhythm in persistent AF. Patients in the irbesartan plus amiodarone combination group had a significantly higher rate of sinus rhythm maintenance at 360 d in comparison to the group on amiodarone alone.

In patients with HF and AF, preablation use of an ACEI resulted in an improved ablation success rate in nonparoxysmal AF with low ejection fraction. In a single center, Mohanty *et al*[9] investigated 703 consecutive patients with preserved left ventricular ejection fraction (LVEF > 45%) and 345 patients with reduced EF (< 45%) undergoing RFA for AF. At 24 ± 7 mo of follow-up, in patients with nonparoxysmal AF and reduced EF, the ACEI pretreatment group had lower recurrence of AF post-RFA compared to the non-ACEI group (76% *vs* 64%, $P = 0.015$). Among paroxysmal AF patients regardless of LVEF, ACEI use was not observed to be associated with improved RFA outcomes (80% *vs* 77%, $P = 0.82$). These findings are similar to our study, which demonstrated that in patients with paroxysmal AF the use of an ACEI or ARB did not affect outcomes and event-free survival following CBA. Currently, the guidelines do not recommend the use of ARB or ACEI for the sole purpose of preventing the recurrence of AF, due to a lack of substantial literature supporting it. However, there is growing evidence that in patients with nonparoxysmal AF undergoing RFA, the use of ACEIs or ARBs decreases the recurrence of AF.

Our study had its inherent limitations. Firstly, it was a single center retrospective study with a small sample size limiting the generalizability of outcomes. Secondly, the study population was underpowered for the detection of benefits in patients with paroxysmal AF. Thirdly, we examined an exclusive population of patients with paroxysmal AF and not persistent AF who are known to have a higher degree of electrical and structural remodeling with the potential for superior benefits with ACEIs/ARBs. Since this was a small retrospective study, we could not perform a power analysis. Lastly, our patient population within the ACEI/ARB group had a higher rate of hypertension and CAD. Although these factors were accounted for in the multivariate analysis, we did not collect the data on whether CAD was optimally treated or required a revascularization procedure. Despite these limitations, our study is the first of its kind to examine the role of ACEI/ARB use in an exclusive population of paroxysmal AF patients undergoing CBA.

## CONCLUSION

In paroxysmal AF patients undergoing CBA, the use of ACEIs or ARBs was not associated with decreased recurrence of AA. Larger, multicenter, controlled studies, particularly in patients with persistent AF and those at risk for significant myocardial fibrosis such as cardiomyopathy, HF or valvular disease are necessary to fully evaluate the effect of ACEIs, ARBs, or angiotensin receptor

neprilysin inhibitors such as sacubitril/valsartan in patients undergoing CBA for AF.

## ARTICLE HIGHLIGHTS

### *Research background*

Cryo-balloon ablation (CBA) is recommended for patients with paroxysmal atrial fibrillation (AF) refractory to antiarrhythmic drugs. However, only 80% of patients benefit from initial CBA.

### *Research motivation*

Myocardial fibrosis is a known risk factor for the development of AF and angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are known agents that prevent remodeling. There is growing evidence that pretreatment with ACEIs and ARBs decreases the recurrence of AF postablation, particularly in nonparoxysmal AF undergoing radiofrequency ablation.

### *Research objectives*

To investigate the role of ACEIs and ARBs in preventing the recurrence of atrial arrhythmia (AA) following CBA for paroxysmal AF.

### *Research methods*

We performed a single-center, retrospective, cross-sectional study. All patients aged 18 years or older, with a diagnosis of paroxysmal AF, undergoing CBA as a first or repeat procedure between January 2015 and April 2018 were included. We followed these patients with paroxysmal AF undergoing CBA for 1 year post-procedure. Recurrence was assessed by documented AA on electrocardiogram or any form of long-term cardiac rhythm monitoring.

### *Research results*

After 1-year follow-up, out of 103 patients, 19 (18.4%) developed recurrence of AA. Of these, 42 patients were receiving ACEIs/ARBs at the time of CBA. 21 (58%) patients were taking ACEIs and 15 (42%) ARBs. Patients on ACEIs/ARBs had a greater prevalence of hypertension and coronary artery disease. On a multivariate model adjusted for baseline demographics and risk factors for AF, ACEI or ARB therapy did not prevent the recurrence of AA following CBA ($P$ = 0.72). Similarly, on Kaplan–Meier analysis pretreatment with ACEIs/ARBs did not predict the time to first recurrence of AA ($P$ = 0.2173).

### *Research conclusions*

In paroxysmal AF patients undergoing CBA, the use of ACEIs or ARBs was not associated with decreased recurrence of AA.

### *Research perspectives*

Future studies, particularly in patients with persistent AF and those at risk for significant myocardial fibrosis such as cardiomyopathy, heart failure or valvular disease are necessary to fully evaluate the effect of ACEIs, ARBs, or angiotensin receptor neprilysin inhibitors such as sacubitril/valsartan in patients undergoing CBA for AF.

## FOOTNOTES

**Author contributions:** Al-Seykal I and Bose A contributed to the conceptual design of the study; Al-Seykal I, Bose A, Mishra A and Hashmath Z independently screened the medical records and extracted the data; Chevli P did the statistical analysis; Al-Seykal I, Mishra A, Hashmath Z and Sharma N contributed to write-up and submission of the study; Bose A, Mishra A, and Laidlaw D reviewed the final manuscript; all authors reviewed and agreed with the final content of the article.

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of MetroWest Medical Center.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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SYSTEMATIC REVIEWS

# Virulent endocarditis due to *Haemophilus parainfluenzae*: A systematic review of the literature

Abdulbaril Olagunju, Jake Martinez, Dorothy Kenny, Philip Gideon, Farouk Mookadam, Samuel Unzek

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**Peer-review model:** Single blind

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## Abstract

### *BACKGROUND*

*Haemophilus parainfluenzae* (HPI) belongs to the HACEK (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella* spp., and *Kingella* spp.) group of organisms. The HACEK group of organisms are a part of the oropharyngeal flora and can cause invasive opportunistic infection such infective endocarditis (IE) in hosts with compromised immunological barriers.

### *AIM*

To perform a 20-year systematic review of the literature characterizing the clinical presentation, epidemiology and prognosis of HPI IE.

### *METHODS*

We performed a systematic review of Medline, Pubmed, Scopus and Embase from 2000 to 2022 to identify all cases of HPI IE.

### *RESULTS*

Thirty-nine adult cases were identified. HPI IE was found to affect males slightly more than females and is common in patients with predisposing risk factors such as underlying valvular abnormalities. It mostly affected the mitral valve and had an indolent course; significantly sized vegetations (> 1 cm) developed in most cases. Central nervous system septic embolization was common. It had a favorable prognosis compared to staphylococcal and streptococcal IE.

### *CONCLUSION*

Clinicians should be attentive to the indolent course of HPI IE and the presence of

predisposing risk factors in order to allow for timely management.

**Key Words:** *Haemophilus parainfluenzae*; Infective endocarditis; Mitral valve; Vegetation



**Core tip:** This review and illustrative case show a temporal change in the epidemiology of *Haemophilus parainfluenzae* (HPI) infective endocarditis in 2000–2022. Compared with a review of 26 HPI endocarditis cases from 1984–1995 by Darras-Joly *et al*, this review reported younger mean age, similar rate of infection in both genders, shorter time to diagnosis, higher association with intravenous drug use (IVDU), higher rate of embolic events in general, and tricuspid and pulmonic valve involvement. The rate of mitral valve involvement has remained steady over the past three decades, while there has been a decrease in the rate of aortic valve involvement. There has been a decrease in valvular vegetation rates and incidence of congestive heart failure as complications, while the mortality rate remained similar. These findings indicate improvement in diagnosis and treatment of HPI over the past three decades; however, they also suggest an increase in its virulence and an association with the rising rate of IVDU highlighted by the involvement of the right-sided heart valves.

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## INTRODUCTION

Infective endocarditis (IE) remains a significant cause of morbidity and mortality. The incidence has increased from 5–7 cases per 100000 of the population in 2000 to 15 cases per 100000 person-years in 2011[1-3]. Common risk factors include an immunocompromised state, intravenous drug use (IVDU), underlying valvular disorders, prosthetic valves, and implanted cardiac devices[1-3]. The microbiology of IE is important and affects clinical presentation and prognosis[1-3]. Skin flora, including *Staphylococcus*, *Enterococcus* and *Streptococcus* spp., are the most common causative organisms in IE, accounting for 80%–90% of cases, with a mortality rate as high as 30%[1-3].

Although less common, the oropharyngeal flora is also an important cause of IE, particularly the HACEK (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella* spp., and *Kingella* spp.) group[1,4-6]. This group has been identified in 1.5%–2% of all IE cases, with a mortality rate of 2%[4-6]. They are fastidious Gram-negative bacilli known for their slow growth in routine blood culture media, which may cause a delay in diagnosis[4,5]. Reported risk factors for the development of HACEK group IE include recent dental procedures and abnormal heart valves[4,5]. The most common organism implicated is *Aggregatibacter* spp[4,6]; however, IE due to *Haemophilus parainfluenzae* (HPI) is gaining increasing attention in the literature. Here, we present an illustrative case of endocarditis in a healthy young man with no predisposing risk factors, and a systematic review of HPI IE cases reported in the literature within the last 20 years to characterize its clinical presentation, epidemiology and prognosis.

### *Illustrative case*

A 25-year-old man with no significant past medical history presented to the emergency department with a 2-mo history of worsening frontal headache and 1 wk of fever and watery diarrhea. Physical examination was significant for a fever of 39.1 °C, heart rate of 109 beats/min, blood pressure of 118/63 mmHg, and holosystolic murmur auscultated at the cardiac apex. Laboratory results were remarkable for white blood count (WBC) count of 12.9 K/L (normal: 4–11), hemoglobin 8.5 g/dL (normal: 13.5–17.0), mean corpuscular volume 77 fL (normal: 78–100), relative distribution width of 16.2% (normal: 11–15), procalcitonin 2.33 ng/mL (normal: 0.49), C-reactive protein 218 mg/L (normal: 4.9), and erythrocyte sedimentation rate 56 mm/h (normal: 0–15). Intravenous (IV) vancomycin, ceftriaxone and acyclovir were initiated due to concern for meningitis. Chest radiograph and head computed tomography were negative for acute abnormalities. A lumbar puncture was performed, with cerebrospinal spinal fluid (CSF) analysis positive for WBC count of 231/mm$^3$ (normal: 0–5), with 67% neutrophils and 21% lymphocytes, glucose 51 mg/dL (normal: 40–70), and protein f 49.9 mg/dL (normal: 15–40). CSF herpes simplex virus polymerase chain reaction was negative, and acyclovir was discontinued.

Blood cultures on hospital day 4 showed Gram-negative rods, which speciated to HPI on hospital day 6. CSF cultures remained negative, and antibiotics were de-escalated to IV ceftriaxone for HPI bacteremia. Additionally, esophagogastroduodenoscopy, colonoscopy and subsequent biopsies were normal. Iron studies were significant for serum iron of 9 g/dL (normal: 40–190), transferrin 119 mg/dL (normal: 200–390), transferrin saturation 6% (normal: 15–50), total iron binding capacity 167.8 g/dL (normal: 250–435), and ferritin 1083 ng/mL (normal: 25–506).

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) revealed two mobile echodensities on the atrial side of the mitral valve, consistent with vegetations on the A2 and P2 segments of the mitral leaflets (Figure 1), with an anterior leaflet perforation and a severe mitral regurgitation (Videos 1 and 2). Magnetic resonance imaging (MRI) of the brain revealed a 1.0  0.5 cm ring enhancing lesion in the right parietal lobe with surrounding vasogenic edema, suggestive of an abscess secondary to septic emboli (Figure 2A). Repeat MRI brain at 4 wk revealed near resolution of the right parietal lobe lesion (Figure 2B). After completing 8 wk of ceftriaxone, he underwent mitral valve repair with edge-to-edge repair of A1 and P1 segments. Postoperative TEE revealed adequate A1 and P1 fusion. The postoperative course was complicated by left-sided proximal muscle weakness and paresthesia, which resolved within 48 h. He completed cardiac rehabilitation successfully and had no further complications.

## MATERIALS AND METHODS

### Data sources and searches

Two authors (AO and DK) independently searched Medline, Pubmed, Scopus, Embase and Reference Citation Analysis from January 1, 2000 to March 30, 2022 using the following keywords: *Haemophilus parainfluenzae* and infective endocarditis. An independent search was conducted by a qualified librarian using similar terms. Only articles published in English were included.

### Article selection

Inclusion criteria included IE due to HPI, patients aged > 18 years, positive blood or pathology specimens for HPI, and clinical and echocardiographic evidence of IE. Articles not meeting these criteria were excluded. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[7] (PRISMA 2009 Checklist).

### Data extraction

Extracted data included patient demographics (age and gender), symptoms at initial presentation, comorbidities (prior valvular disorder, structural heart defects, recent dental, and gastrointestinal or genitourinary procedures), affected valves, severity of valvular damage, patient management, and complications.

### Data analysis

We conducted a qualitative systematic analysis using descriptive statistics. A meta-analysis could not be performed due to the differences among individual cases and the small sample sizes (*i.e.* 1 patient) included in the case reports.

## RESULTS

### Search results and article inclusion

Our initial search generated 383 articles. After excluding 221 duplicates, the remaining 162 articles were screened for inclusion (Figure 3). Of these, 39 articles[8-46] were systematically reviewed. The remaining articles were excluded because they were irrelevant to the topic (36 articles), discussing IE with organisms other than HPI (52 articles), review articles on HACEK organisms and IE (13 articles), pediatric case reports on HPI IE (12 articles), or not published in English (3 articles).

### Patient characteristics

**Age and gender:** A total of 39 patients were identified. The mean age was 39 years, with a range of 18–69 years. There was a slight predominance towards men (52.5%).

**Predisposing risk factors for IE:** Approximately 10% of the patients reported a history of IE. About 17.5% had a history of valve replacement (4 with bioprosthetic valves, 2 with mechanical valves, and 1 with unspecified valve type). Twenty percent had mitral valve disorders (3 with mitral valve prolapse, 2 with rheumatic heart disease, and 1 with mitral regurgitation). Eighteen percent had aortic valve disorders (3 with bicuspid aortic valve and 3 with aortic stenosis). Current IVDU was reported in 17.5%. Approximately 10% had poor dentition. Thirteen percent had a history of pacemaker and implanted

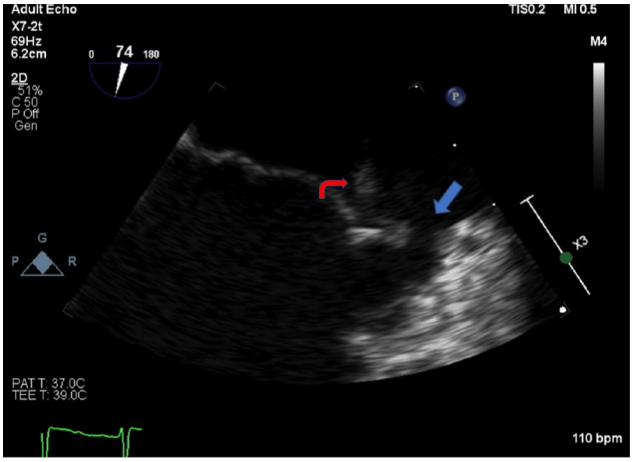


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**Figure 1 Zoomed mid-esophageal view on transesophageal echocardiography, showing an echodensity attached to the A2 segment of the anterior leaflet of the mitral valve (red arrow) with evidence of leaflet perforation in the A1 segment (blue arrow).**

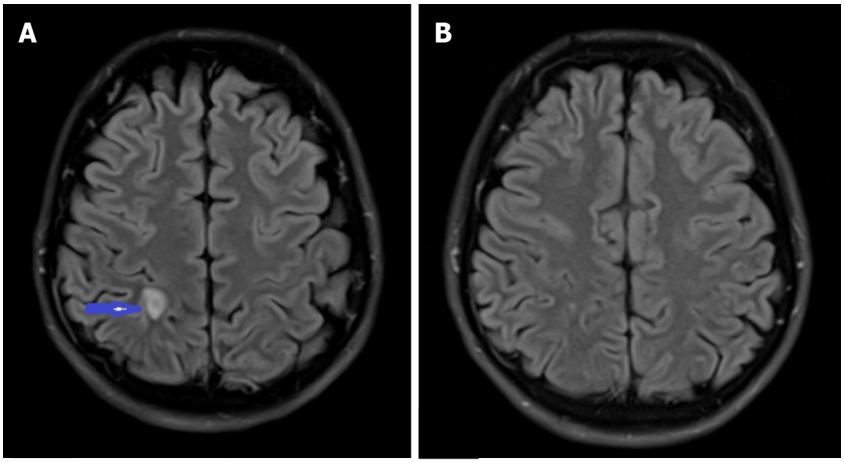


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**Figure 2 Septic embolus in the brain.** A: T2-weighted MRI brain showing a 1.0 cm × 0.5 cm ring enhancing lesion (blue arrow) in the right parietal lobe with central diffusion restriction and mild surrounding vasogenic edema; B: Repeat MRI brain with near complete resolution of the ring enhancing lesion. MRI: Magnetic resonance imaging.

cardiac defibrillator placement. Two patients had a recent gastrointestinal or genitourinary tract procedure. Three patients were immunocompromised, 2 of which were pregnant (Table 1). Seven of the 39 patients had no predisposing risk factors.

**Presenting symptoms and signs:** The most common presenting symptom was fever, reported in most patients (36 patients), followed by fatigue (25 patients). Seven patients had shortness of breath, and four reported weight loss. Twenty-eight of 39 patients also presented with one or more manifestations of septic emboli, including embolic stroke (20 patients), septic pulmonary embolism (4 patients), renal emboli (2 patients), and splenic infarct (3 patients). Cutaneous manifestations were noted including Janeway lesions (3 patients), splinter hemorrhages (4 patients), petechiae or purpura (2 patients), or Osler nodes (1 patient) (Table 1).

**Valve involvement:** Valvular regurgitation was by far the most common abnormality; reported in 28 patients. Of these, 14 had severe regurgitation, eight had moderate regurgitation, and two had mild regurgitation. Mitral regurgitation and stenosis were reported in one case, and mitral valve prolapse was reported in one case. The mitral valve was the most common valve to be affected; noted in 28 patients. Eight patients had aortic valve involvement. The tricuspid valve was affected in seven patients, and only one patient had pulmonary valve involvement (Table 1).

**Echocardiography:** TTE was the main diagnostic modality, utilized in 36 (90%) patients, followed by TEE for confirmation in 33 patients. Valvular vegetations were reported in 23 patients, with an

**Table 1 Compares the characteristics of infective endocarditis caused by *Haemophilus parainfluenzae* in this systematic review with the review by Darras-Joly *et al*[58]**

| Characteristics | | Present review, *n* (%) | Previous review, *n* (%) |
|---|---|---|---|
| Mean duration from sx to dx | | 18.9 (3-49) d | 28.2 (5-80) d |
| Demographics | Age, yr (range) | 39 (18-69) | 43.9 (21-79) |
| | Male-to-female ratio | Approximately 1:1 | Approximately 2:1 |
| Predisposing risk factors | History of IE | 4 (10) | 1 (3.8) |
| | Valve disorder and/or replacement | 10 (25) | 18 (69.2) |
| | IVDU | 8 (20) | 1 (2.4) |
| | Poor dentition | 4 (10) | NR |
| | Cardiac devices | 5 (13) | 4 (15.4) |
| | History of recent GI/GU procedure | 2 (5) | NR |
| | Immunocompromised | 3 (8) | 3 (7.1) |
| Symptoms and signs | Fever | 36 (90) | 40 (95.2) |
| | Fatigue | 24 (60) | NR |
| | Vegetations | 24 (60) | 19 (73.1) |
| | Abscesses | 7 (17.5) | 2 (7.7) |
| | Embolic events | 29 (73) | 15 (35.7) |
| | CNS | 20 (50) | 9 (21.4) |
| | Lungs | 4 (10) | 2 (4.8) |
| | Spleen | 3 (7.5) | 2 (4.8) |
| | Kidney | 2 (5) | 1 (2.4) |
| Valves affected | Mitral | 29 (73) | 19 (73) |
| | Aorta | 8 (20) | 8 (30.7) |
| | Tricuspid | 7 (17.5) | 1 (3.8) |
| | Pulmonic | 1 (2.5) | 0 (0) |
| | Multiple valves | 6 (15) | 3 (11.5) |
| Outcomes | Recovery with antibiotics and/or surgery | 35 (88) | NR |
| | CHF | 3 (8) | 13 (30.9) |
| | Death | 2 (5) | 2 (4.8) |

CHF: Congestive heart failure; dx: Diagnosis; GI: Gastrointestinal; GU: Genitourinary; IVDU: Intravenous drug use; IE: Infective endocarditis; sx: Symptoms; NR: Not reported.

estimated mean size of 1.9 cm. Cardiac abscesses were reported in 17.5%, but abscess size was reported in only one of the cases as 1.6  1.8 cm. The abscess locations included the aortic root, mitral–aortic intervalvular fibrosa, near a prosthetic aortic valve, left ventricular endocardium, and myocardium. Three patients developed a fistulous connection between the atrium and ventricle. Valvular perforation was reported in 2 cases.

**Treatment:** The majority (28 patients) were treated both medically and surgically. Nine patients underwent valve repair, while six underwent replacement. Two patients underwent pacemaker removal. Eleven patients had unspecified surgical intervention. Sixty-two percent of patients were treated with ceftriaxone. Ten percent received other antibiotics including levofloxacin, ciprofloxacin, gentamicin, cefotaxime and rifampin. The antibiotic therapy utilized in the remaining 28% of patients was not specified.

**Outcome:** Two patients reportedly developed congestive heart failure (CHF) and two patients died. The remaining 35 patients recovered adequately.

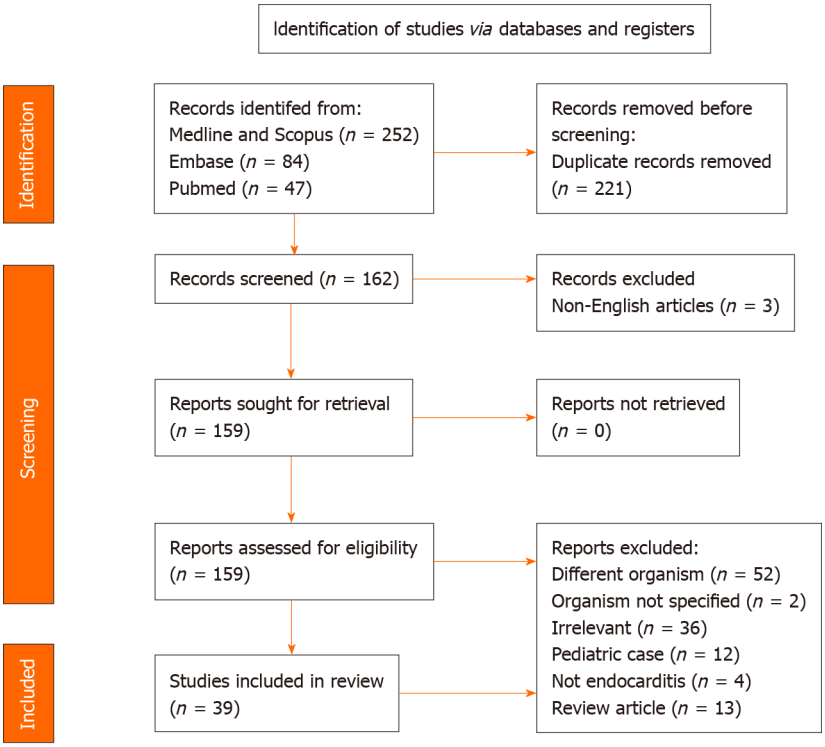


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**Figure 3 PRISMA flow chart highlighting article search and selection.**

## DISCUSSION

HPI is a part of the oropharyngeal and genitourinary tract flora and has been implicated as a cause of opportunistic infections such as meningitis, IE, and septic arthritis[47]. It is a fastidious Gram-negative coccobacillus and belongs to the genus *Haemophilus* which consists of the *H. influenzae*, *H. parainfluenzae* and *H. ducreyi* groups[47]. They require beta-nicotinamide adenine dinucleotide (NAD) and/or heme to supplement *in vitro* growth[47]. An important differentiating feature of HPI is its ability to synthesize heme and hence does not require heme supplementation to grow[47].

The virulence of HPI is not well characterized[47,48]. In general, the *H. parainfluenzae* group has some degree of resistance to beta-lactam antibiotics, particularly penicillins[47,48]. Isolates have been identified that are multidrug resistant to tetracyclines, fluoroquinolones and macrolides[47]. The mechanisms behind this resistance are due to mutations in the penicillin-binding protein, Tet, DNA gyrase, topoisomerase, and 50s ribosomal protein genes[47,49]. The antibiotics with adequate minimum inhibitory concentration on HPI include levofloxacin, cefditoren, cefotaxime and cefpodoxime, although other antibiotics such as aminoglycosides and chloramphenicol may have adequate effect[50,51]. Culturing HPI involves addition of patients' blood samples to a brain–heart infusion with 5% beef extract broth, which is incubated at 37 °C for up to 14 d[52]. Gram-negative coccobacilli are identified *via* Gram stain and inoculated onto a peptone–protease agar[52]. Paper discs containing NAD and heme are applied to the agar which incubates overnight[52]. HPI is then identified based on its sole reliance on the presence of NAD for growth[52]. Additionally, the 16S rRNA polymerase chain reaction and mass spectrometry are reliable means of differentiating *Hemophilus* spp. and the HACEK organisms without culturing[18].

In our review, the majority of patients had at least one predisposing risk factor for IE, such as a history of IE, an underlying valve disorder, a prosthetic or mechanical valve or a cardiac device, poor dentition, recent dental procedure within 2 wk, IVDU, or an immunocompromised state (including use of steroids or pregnancy). This is important for clinicians to recognize, as eradication or control of the predisposing factor may help prevent recurrent HPI infection.

The average duration between symptom onset and diagnosis was 18.9 d, and surgical intervention (due to the presence of large vegetations ~2 cm) was required in most of the patients (69%). These features highlight the indolent course of HPI IE and signify the need for prompt diagnosis, which may reduce the need for surgical intervention. The resolution of IE with cephalosporin, aminoglycoside and fluoroquinolone antibiotics suggests that the majority of HPI bacteria in the past 20 years are not multidrug resistant.

The risk of embolic events in IE is common with *Staphylococcus aureus*, *Candida* spp., and HACEK organisms[51]. The reported incidence ranges between 28% and 66% for *S. aureus*, with central nervous

system (CNS) embolism being the most common[53,54]. In this review, ~70% of embolic complications were in the CNS. This is notable as previously, *Kingella* spp. appeared to have the highest rate of CNS embolism of all HACEK organisms, with a rate of 20%–30%[55]. Embolic events have been associated with worse prognosis in IE, with the risk proportional to vegetation size > 10 mm[53,54]. The indolent or subacute course of HPI IE may explain why the mortality remains lower compared to IE involving other organisms, despite significant vegetation size. The in-hospital mortality rates of *S. aureus* and *Streptococcus* spp. IE are 20%–30% and 11%, respectively[53,56]. The mortality rate of HPI IE in this review was 5%. Of the HACEK organisms that cause IE in adults, *Actinobacillus actinomycetemcomitans* (a member of the *Aggregatibacter* spp.) and *Cardiobacterium* spp. have the highest reported mortality rates of 18% and 10%, respectively[57,58]. While both are associated more with aortic valve endocarditis[57,58], HPI more commonly affects the mitral valve.

Our findings and the illustrative case show a temporal change in the epidemiology of HPI within 2000–2022. Compared to a review of 26 HPI endocarditis cases from 1984 to 1995 by Darras-Joly *et al* [58], this review reported a younger mean age, similar rate of infection in both genders, shorter time to diagnosis, higher association with IVDU, higher rate of embolic events, and tricuspid and pulmonic valve involvement. The rate of mitral valve involvement has remained steady over the past three decades, while there has been a decrease in the rate of aortic valve involvement. Valvular vegetation rates and CHF incidence have decreased, while the mortality rate remained similar (Table 1). These findings might indicate the improvement in the diagnosis and treatment of HPI over the past three decades. However, the increased involvement of right-sided valves suggests an increase in its virulence and an association with the rising rate of IVDU. Notably, the review by Darras-Joly *et al*[58] was not systematic because it was limited to cases in France. To the best of our knowledge, this is the first systematic review HPI IE to be published in the English language literature.

Our patient's presentation of subacute IE highlights the typical features of HPI IE. It is indolent, has a predilection for the mitral valve, and is commonly associated with septic emboli involving the CNS. However, multiple features were present suggesting HPI may be more virulent in the current era, including the patient's absence of risk factors, HPI induced leaflet perforation (which was not noted in our review), and valvular destruction requiring surgery.

### Limitations

A noteworthy limitation of this review is that it did not account for unreported cases of HPI IE; therefore, we cannot ascertain an exact incidence and prevalence.

## CONCLUSION

This systematic review of reported adult HPI IE cases spanning the last two decades highlights the subacute course of HPI IE, its preference for the mitral valve, and favorable prognosis compared to IE caused by the other HACEK organisms, *Staphylococcus*, and *Streptococcus*. Clinicians should be attentive to its indolent course and the presence of predisposing risk factors in order to allow for timely management.

## ARTICLE HIGHLIGHTS

### Research background

Existing data indicate that the incidence of infective endocarditis (IE) continues to rise steadily. Although components of the skin flora including *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. are the most implicated organisms particularly in virulent IE, the oropharyngeal flora including the HACEK group of are a significant cause of IE.

### Research motivation

An interesting presentation of *Haemophilus parainfluenza* (HPI) IE in a 25-year-old man with no significant past medical history and no predisposing risk factor for IE was the basis for this systematic review. It aimed to determine if there have been temporal changes in the presentation and prognosis of IE caused by HPI over the past two decades.

### Research objectives

To characterize the risk factors, signs and symptoms, echocardiographic findings and the prognosis of IE caused HPI.

### Research methods

A search of Medline, Pubmed, Scopus and Embase was conducted to identify the cases of HPI IE

published in 2000–2022. A systematic review of these cases was performed to analyze the trends in the presentation and prognosis of HPI IE.

### Research results

This systematic review of 39 HPI IE cases in the English literature highlights the slight male predominance of the disease, the nonspecific presentation with constitutional symptoms, the predilection for the mitral valve, a high rate of central nervous system embolic events and a lower mortality rate compared to IE caused by microbes of the skin flora.

### Research conclusions

HPI IE is an indolent disease that requires a high index of suspicion to diagnose and is associated with a favorable prognosis with timely intervention.

### Research perspectives

We have illustrated a case and conducted a two-decade systematic review of the HPI IE cases published in the English language literature. In doing so, we have highlighted its indolent course, presentation and prognosis. We have also compared our findings with those of a review of HPI IE cases between 1984 and 1995; in doing so, we have enumerated some temporal changes in this disease entity. These include a younger mean age of presentation, identical rate of infection between males and females, improvement in diagnosis, a higher rate of embolic events and an increasing association with intravenous drug use.

## FOOTNOTES

**Author contributions:** Olagunju A and Mookadam F designed the research; Olagunju A, Kenny D, Martinez J, Gideon P, and Unzek S performed the research; Olagunju A, Kenny D and Mookadam F analyzed the data; Olagunju A, Kenny D, Martinez J and Mookadam F wrote the paper.

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**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



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LETTER TO THE EDITOR

# Is Takotsubo cardiomyopathy still looking for its own nosological identity?

Riccardo Scagliola, Gian Marco Rosa

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## Abstract

Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this remains an unresolved matter in clinical practice. Several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of myocardial infarction with non-obstructive coronary arteries. Further investigations are needed in order to define TCM with the most appropriate disease taxonomy.

**Key Words:** Takotsubo cardiomyopathy; Myocardial infarction with non-obstructive coronary arteries; Disease classification



**Core Tip:** Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this remains an unresolved matter in clinical practice. Several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of myocardial infarction with non-obstructive coronary arteries. These issues need to be confirmed by further investigations, in order to define TCM with the most appropriate disease taxonomy.

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## TO THE EDITOR

Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this remains an unresolved matter in clinical practice. Current revised Mayo Clinic diagnostic criteria for TCM include: (1) The presence of transient left ventricular wall motion abnormalities (either hypokinesis, akinesis or dyskinesis) with or without apical involvement; (2) usually extending beyond a single epicardial vascular distribution; (3) in the absence of obstructive coronary artery disease on coronary angiography; (4) associated with new electrocardiographic abnormalities or modest troponin increment; and (5) in the absence of pheochromocytoma or myocarditis[1]. Subsequently, the International Takotsubo Diagnostic Criteria (interTAK Diagnostic Criteria) provided the following additional criteria in order to improve the identification of TCM: (1) Cases with wall motion abnormalities related to the distribution of a single epicardial coronary artery should not be considered an exclusion criteria of TCM; (2) pheochromocytoma, as well as neurologic disorders (*i.e.* subarachnoid hemorrhage, ischemic stroke or transient ischemic attack) are recognized as secondary causes of TCM, and (3) the presence of coronary artery disease does not represent an exclusion criterion of TCM[2]. This latter additional finding and the contextual detection of obstructive epicardial coronary lesions make the distinction between acute coronary syndrome and TCM more challenging in clinical practice[3]. In this regard, whether TCM should be classified as a distinct subset of myocardial infarction with non-obstructive coronary arteries (MINOCA) is still controversial. In a comprehensive review by Vidal-Perez *et al*[3], TCM was included within the wide nosological spectrum of MINOCA. However, emerging clinical and pathophysiologic findings in the literature have progressively raised doubts concerning this current taxonomy. In a retrospective analysis conducted by Lopez-Pais *et al*[4] on a large multicenter registry, patients with TCM showed a different clinical profile compared to those belonging to the other subsets of MINOCA. Specifically, TCM was more frequently detected as an intercurrent complication during hospitalization for other causes, and was characterized by a much more aggressive acute phase and by a better long-term prognostic outcome, compared to patients affected by the other forms of MINOCA. Additionally, when present, some electrocardiographic findings can also help to distinguish between TCM and the other subsets of MINOCA. In particular, the absence of Q waves or reciprocal changes of ventricular repolarization, a ratio between ST-segment elevation in leads $V_4$-$V_6$ and $V_1$-$V_3$ > 1 and the presence of ST-segment depression in lead aVR in the absence of ST-segment elevation in lead $V_1$ have been reported to detect TCM with a high predictive accuracy[5,6]. Furthermore, different pathophysiological processes have been shown to be involved in developing reversible wall motion abnormalities which characterize TCM, compared to the rest of MINOCA subsets (Table 1). Although microvascular dysfunction has been hypothesized to be involved in the pathogenic mechanisms of TCM, it seems to represent a mere epiphenomenon compared to the catecholaminergic surge related to sympathetic hyperactivity, which is mediated by both the central and autonomic nervous system in response to psychophysical or environmental stressors[7]. Specifically, direct catecholamine toxicity and the effects of norepinephrine spillover from the cardiac sympathetic nerve terminals, have been shown to be the greatest responsible mechanisms of wall motion abnormalities detected in TCM, as demonstrated by the congruent distribution of cardiac nervous terminals to the affected segments of the myocardial wall[8]. This is reflected in a typical histopathological pattern called myocytolysis, which is characterized by areas of early myofibrillar damage, hypercontracted sarcomeres and a mononuclear inflammatory response. These histological features are distinct from those noted in the rest of patients with MINOCA (which were instead characterized by atonic myocytes, with no myofibrillar damage and polymorphonuclear infiltrates), and were not primarily induced by vasoconstriction, but by a direct effect of catecholamines on cardiac β-adrenergic receptors (like other conditions related to the catecholamine surge, as in the case of pheochromocytoma or subarachnoid hemorrhage)[9,10]. As reported by Santoro and coworkers, histologic findings confirm how TCM and acute coronary syndromes are sustained by two different inflammatory patterns. In particular, high levels of anti-inflammatory interleukins detected in TCM (particularly IFN-α and IFN-γ) have been shown to be related to the presence of M2 macrophages surrounding the impaired myocardial tissue, and to their capability in removing damaged cells and preserving healthy tissue, thus favoring a complete functional recovery in this subset population[11]. Finally, the presence of transient and reversible transmural myocardial edema involving the dysfunctional wall segments on T2-weighted imaging, in the absence of late gadolinium enhancement, represents a pathognomonic hallmark provided by cardiac magnetic resonance in TCM patients, compared to the rest of MINOCA subjects[12]. In conclusion, several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of MINOCA. These issues need to be confirmed by further investigations, in order to define TCM with the most appropriate disease taxonomy.

**Table 1 Characterizing the differences between Takotsubo cardiomyopathy and myocardial infarction with non-obstructive coronary arteries**

| | Takotsubo cardiomyopathy | MINOCA |
|---|---|---|
| Clinical findings | A more aggressive acute phase despite a better long-term cardiovascular prognosis | A less aggressive acute phase despite a worse long-term cardiovascular prognosis |
| Main pathophysiologic mechanisms | Sympathetic hyperactivity and a direct effect of catecholamines on β-adrenergic receptors of cardiomyocytes | Coronary plaque disruption; Coronary vasospasm; Spontaneous coronary artery dissection; Microvascular dysfunction; Coronary thromboembolism |
| Histopathologic lesions | Areas of myofibrillar damage with hypercontracted sarcomeres and mononuclear infiltrates | Absence of myofibrillar damage with atonic sarcomeres and polymorphonuclear infiltrates |
| Location of myocardial lesions | Around intracardiac nervous terminals | Around cardiac vessels |
| Inflammatory patterns | Increased levels of anti-inflammatory interleukins, able to remove damaged cells and preserve healthy myocardial tissue | Increased levels of pro-inflammatory interleukins, able to promote coronary plaque disruption and microvascular impairment |
| CMR findings | Transient and reversible transmural myocardial edema on T2-weighted imaging in the absence of late gadolinium enhancement | Late gadolinium enhancement (either subendocardial or transmural) with or without myocardial edema on T2-weighted imaging |

CMR: Cardiac magnetic resonance; MINOCA: Myocardial infarction with non-obstructive coronary arteries.

## FOOTNOTES

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LETTER TO THE EDITOR

# Euglycemic diabetic ketoacidosis: A rare but serious side effect of sodium-glucose co-transporter 2 inhibitors

Nenad Lakušić, Ivana Sopek Merkaš, Ana Marija Slišković, Dora Cerovec

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## Abstract

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication and from recently established therapy in chronic heart failure patients. A rare, but potentially life-threatening complication of SGLT2 inhibitor use is euglycemic diabetic ketoacidosis. We described a case of a middle-aged male patient with type 2 diabetes who developed metabolic ketoacidosis after a few days of empagliflozin administration. SGLT2 inhibitor related ketoacidosis presents with euglycemia or only modestly elevated glucose blood concentrations, which causes delayed detection and treatment of ketoacidosis. There are multiple possible risk factors and mechanism that might contribute to the pathogenesis of ketoacidosis. It is implied that SGLT2 inhibitor use and prescription by non-diabetologists (cardiologists, nephrologists, family physicians, *etc.*) will continue to grow in the future. It is important to inform the general cardiac public about this rare but serious side effect of SGLT2 inhibitors.

**Key Words:** Sodium-glucose co-transporter 2 inhibitors; Euglycemic diabetic ketoacidosis; Chronic heart failure

**Core Tip:** Sodium-glucose co-transporter 2 inhibitors have recently become an established treatment for most chronic heart failure (CHF) patients (with and without diabetes), and it is important for the cardiologist to know their side effects, including those that are rare, but serious, like euglycemic ketoacidosis. In this way, an unwanted outcome of CHF treatment can be avoided.

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## TO THE EDITOR

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication which decrease the reabsorption of glucose in the renal tubules, causing urinary glucose excretion and thereby modestly lowering elevated blood glucose levels in patients with type 2 diabetes. The SGLT2 receptors are expressed in the proximal tubule of the kidney and mediate reabsorption of 90% of the filtered glucose load. By their mechanism of action, SLGT2 inhibitors also modestly decrease blood pressure (osmotic diuresis) and weight (reduction in adipose tissue as well as calorie loss through glycosuria)[1].

According to the latest European Society of Cardiology guidelines on chronic heart failure (CHF)[2], SGLT2 inhibitors (empagliflozin, dapagliflozin) are equally used along with other established therapy for CHF. They can be used in patients with reduced, but also preserved (empagliflozin) ejection fraction of left ventricle, with or without diabetes[3]. The SGLT2 inhibitors achieve beneficial effects by lowering blood pressure, stimulation of natriuresis and diuresis, neurohormonal effect, improvement of cardiac energy metabolism, reduction in inflammation, *etc.*[4]. SGLT2 inhibitors improve cardiovascular outcomes and have a similar effect as a group of drugs in preventing HF and chronic kidney disease progression (class effect), efficacy in secondary prevention of atherosclerotic cardiovascular disease events (empagliflozin and canagliflozin) and in preventing cardiovascular mortality (empagliflozin)[5].

Euglycemic diabetic ketoacidosis[6] is a known and rare complication of SGLT2 inhibitor use and can potentially lead to a life-threatening situation, especially if not recognized in time[7]. Shortly, we would like to describe a case of middle-aged male patient with type 2 diabetes, without CHF, who developed metabolic ketoacidosis after a few days of empagliflozin administration.

The patient is a 42-year-old male with a history of type 2 diabetes treated with metformin for three years, which he took very irregularly. One week before hospitalization, he was administered the combination of empagliflozin 12.5 mg/metformin 1000 mg twice daily. Two days after starting the medication he reported nausea and diarrhea, then vomiting with a feeling of fatigue and malaise. Diabetic ketoacidosis (ketonuria 8 mmol/L, arterial blood gas (ABG) analysis-pH 7.23, glucose 9.7 mmol/L) was diagnosed and the patient was urgently hospitalized. Parameters of renal function and serum kalium level were within referent range. Metabolic acidosis was successfully managed after two days of standard treatment (prompt fluid resuscitation with crystalloid solutions and monitoring of electrolyte and ketones, low-dose intravenous insulin) and omission of empagliflozin from further therapy. On the third day of treatment, the patient was discharged from the hospital with new recommended therapy-basal and fast-acting insulin and metformin.

Diabetic ketoacidosis is a complex metabolic disorder characterized by hyperglycemia, acidosis, and ketonuria, which usually develops in patients with diabetes when insulin levels are too low (absolute or relative insulin deficiency that is accompanied by an increase in counter-regulatory hormones, *i.e.*, glucagon, cortisol, *etc.*). In the absence of insulin, lipolysis is stimulated instead of glycogenolysis for energy production, consequently increasing ketone levels followed by their accumulation in the blood leading to acidosis. Diabetic ketoacidosis most commonly occurs in patients with type 1 diabetes and is usually accompanied by high blood glucose levels[8]. Increased risk of ketoacidosis was described among SGLT2 patients and several mechanisms might contribute to the pathogenesis-SGLT2 inhibitors decrease glucose level by an insulin-independent mechanism, increase the rates of lipolysis in adipose tissue and ketogenesis in the liver (increasing circulating ketone body levels), increase plasma glucagon levels, increase preproglucagon gene expression by acting directly upon pancreatic α-cells, and also SGLT2 inhibitors could decrease renal clearance of ketone bodies (*e.g.*, phlorizin-a nonselective inhibitor of SGLT1 and SGLT2, which increase renal tubular reabsorption of acetoacetate), *etc*[9]. Ketone body levels are elevated in patients receiving SGLT2 inhibitor treatment (and in patients with HF) so it is important to emphasize that failing myocardium in diabetic heart and in HF patients is unable to optimally use traditional substrates (free fatty acid, glucose) but can effectively use ketone bodies as an alternative for energy production. Changes that may include critical effects of SGLT2 inhibitors are those in shifting metabolism from fat/glucose oxidation to ketone bodies and thereby improving

myocardial and renal function[10].

The incidence of ketoacidosis in patients using SGLT2 inhibitors is about 2 per 1000 treated patients [11]. It is important to emphasize that SGLT2 inhibitor–associated ketoacidosis presents with euglycemia or only modestly elevated glucose blood concentrations, which causes delayed detection and treatment of ketoacidosis. Some of the risk factors for developing ketoacidosis in patients treated with SGLT2 inhibitors are prior diabetic ketoacidosis, hemoglobin A1C above 10%, recent hypoglycemia, low baseline serum bicarbonate levels, use of digoxin and medications for dementia[11] or concomitant therapy with pioglitazone[12]. Given that thiazolidinediones, including pioglitazone, can cause fluid retention, as such are contraindicated in patients with NYHA class III and IV heart failure, and are not recommended in patients with symptomatic heart failure[2].

Patients with CHF are a complex group of patients with numerous comorbidities that require specific and differentiated treatment and close monitoring[13]. Since SGLT2 inhibitors have recently become an established treatment for most CHF patients with and without diabetes[2], and their use and prescription by non-diabetologists (cardiologists, nephrologists, and family physicians, *etc*.) will continue to grow in the future. Indeed, there are recommendations and suggestions that SGLT2 inhibitors and beta-blockers might be the first line of treatment for patients with CHF with reduced ejection fraction of left ventricle[14].

Therefore, the main purpose of this letter is to inform and warn the general cardiac public about this rare but serious side effect of SGLT2 inhibitors. In case of nausea, vomiting, or malaise in patients taking SGLT2 inhibitors, prompt response and diagnostic screening are necessary. Serum ketones and ABG analysis should be obtained in any patient presenting these symptoms, and SGLT2 inhibitors should be discontinued if acidosis is confirmed. In this way, serious side effects and an unwanted outcome of CHF treatment can be avoided.

## FOOTNOTES

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