

REVIEWS

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Thromboembolism Associated with Atrial Fibrillation as a Cause of Limb and Organ Ischemia

Powikłania zatorowe w przebiegu migotania przedsionków jako przyczyna niedokrwienia kończyn i narządów wewnętrznych

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Abstract

Atrial fibrillation (AF) is associated with a high risk of thromboembolic episodes. Stroke is the most common embolic complication of AF. Consequently, the majority of the conclusions regarding the association between AF and embolism are based on clinical studies of patients with ischemic stroke. The AF-related thromboembolism of limbs and visceral arteries is rarely recognized, and there is little data on this matter. For this reason it is often a neglected issue. Nevertheless, AF is diagnosed in 60–95% of patients operated on due to acute limb ischemia, 31% of patients with splenic artery embolization, 55% with acute renal ischemia and 47% with mesenteric ischemia. AF should be considered as a leading cause of peripheral embolism. Extracerebral AF-related thromboembolic events are associated with serious clinical consequences including a high mortality rate. This paper reviews the current evidence regarding AF as a cause of visceral and limb ischemia (*Adv Clin Exp Med* 2013, 22, 6, 865–873).

Key words: atrial fibrillation, thromboembolism, limb, organ ischemia.

Streszczenie

Migotanie przedsionków (m.p.) jest związane z dużym ryzykiem wystąpienia incydentów zakrzepowo-zatorowych, wśród których najczęstszym powikłaniem są udary mózgu. W konsekwencji większość wniosków dotyczących korelacji migotania przedsionków z zatorowością opiera się na ocenie stanu klinicznego chorych z udarem niedokrwinnym mózgu. Natomiast zdarzenia zatorowe w przebiegu m.p. prowadzące do niedokrwienia kończyn lub narządów wewnętrznych są rzadziej rozpoznawane. W literaturze niewiele jest danych dotyczących tego rodzaju powikłań i dlatego problem ten jest często niedoceniany przez klinicystów. Migotanie przedsionków jest rozpoznawane w 60–95% przypadków wśród pacjentów operowanych z powodu ostrego niedokrwienia kończyn, występuje u 31% pacjentów z embolizacją tętnicy śledzionowej, u 55% chorych z ostrym niedokrwieniem nerki oraz u 47% pacjentów z niedokrwieniem krezki. W związku z tym m.p. powinno być rozważane jako wiodąca przyczyna zatorowości obwodowej. Incydenty zakrzepowo-zatorowe do tętnic obwodowych występujące w przebiegu m.p. wiążą się z poważnymi następstwami klinicznymi, w tym dużym ryzykiem zgonu. W artykule przedstawiono przegląd aktualnych danych dotyczących związku migotania przedsionków z niedokrwieniem kończyn oraz narządów wewnętrznych (*Adv Clin Exp Med* 2013, 22, 6, 865–873).

Słowa kluczowe: migotanie przedsionków, powikłania zakrzepowo-zatorowe, niedokrwienie kończyn/narządów.

Atrial fibrillation is an arrhythmia whose risk increases significantly with age [1, 2]. Consequently, the prevalence of atrial fibrillation (AF) is continually increasing due to the aging of the population. AF affects 1–2% of the general population, but this value could be an underestimation because of its

asymptomatic course. In a Rotterdam study involving the European population, the overall prevalence of AF was estimated to be as high as 5.5%, including up to 17.8% prevalence in adults over 85 years of age. Furthermore, the lifetime risk of AF in men and women above 55 years of age was estimated at

24.8% and 22.9%, respectively [1]. A Framingham study involving the American population placed the incidence of AF at 0.5% in the age group of 50–60 years, and 8.8% over 80 years [2].

Atrial fibrillation is associated with an increased risk of thromboembolism [3]. The thromboembolic complications of AF are an important cause of morbidity and mortality. Although the embolic complications associated with AF can affect any of the arteries, cerebral arteries are the most frequently occluded vessels. Stroke is then the most common complication of AF. Consequently, the literature database for AF embolic complications mostly concerns ischemic strokes. The information on peripheral artery embolization in the course of AF is limited and, therefore, the data pertaining to this complication is relatively poorly recognized. Most of the few studies regard AF as one of the many factors of peripheral arterial occlusion. Angiosurgical experience indicates that acute limbs and/or visceral ischemia usually occur in patients with cardiac diseases, and AF is the most frequent cause of thromboembolism. The results of existing studies suggest that clinicians may underestimate the problem of extracerebral AF-related thromboembolism, which leads to delayed or mistaken diagnosis.

Risk Factors of Thromboembolic Complications Associated with Atrial Fibrillation

In 2010, the European Society of Cardiology introduced new clinical guidelines for the assessment of the risk of stroke and other thromboembolic episodes. According to the new CHA₂DS₂-VASc score, age ≥ 75 years, history of stroke, transient ischemic attack (TIA) or other thromboembolic episodes are considered as major risk factors (worth 2 points). Non-major risk factors (worth 1 point) include congestive heart failure, left ventricular systolic dysfunction (defined as LVEF $\leq 40\%$), hypertension, diabetes, female gender, age 65–74 years, and vascular disease (history of myocardial infarct, atherosclerotic peripheral artery disease or complex aortic plaque). The one-year risk of stroke in patients with AF, according to the CHA₂DS₂-VASc score, ranges between 0% (for 0 point) and 15.2% (for 9 points) [3].

According to Ciocârliu et al., who analyzed a group of 415 patients with AF, the most common risk factors of embolism included a history of heart failure, arterial hypertension, female gen-

der, and age above 75 years. Most of patients had at least 2 risk factors [4].

The results of certain studies suggest that female gender can be an independent risk factor of embolism associated with AF, both in younger and older age groups. The predisposition of the female gender to embolism may be associated with differences in the coagulation process and endothelial function. Women with AF were characterized by higher concentrations of the F1.2 prothrombin fragment, von Willebrand factor, and tissue plasminogen activator antigen [5]. However, no evident association between the above factors and the increased risk of embolic complications associated with AF has been identified thus far. Additionally, a relationship between the risk of embolism and differences in the structure of the left ventricle in women has been suggested. Previous studies revealed that estrogen-based hormone replacement therapy increases the risk of ischemic stroke in postmenopausal women. However, this relationship was not confirmed in the study by Fang et al. [5]. The study comparing cerebral vs. extra-cerebral embolisms indicated a significantly higher percentage of women in the group with peripheral ischemia (71%) than with stroke (45%) in patients with AF [6].

The analysis of risk factors for extra-cerebral thromboembolism (aorta, renal, mesenteric, pelvic and extremity arteries) for a person in the Atrial Fibrillation Cohort (1980–1993) vs. the Danish population indicated that the highest risk was observed during the 1st year after an incident of AF diagnosis. The higher relative risk of embolism was observed in both women and men with peripheral atherosclerosis, acute myocardial infarct and stroke. Diabetes was the most important risk factor of embolism in men, hypertension and congestive heart failure in women [7].

Recent evidence underlines the importance of echocardiography in the risk assessment of thromboembolic episodes associated with AF. Transesophageal echocardiography (TEE) significantly increases the sensitivity of the detection of left atrial appendage thrombus. The presence of thrombus in the left atrium, reduced left ventricular ejection fraction, left atrial appendage emptying velocity, decreased blood flow velocity in the left atrial appendage (< 20 cm/s), increased left atrial volume index, and the phenomenon of spontaneous echocardiographic contrast (SEC) are important prognostic factors for thromboembolic complications [8–10]. TEE is also helpful in the diagnosis of an AF-independent risk of embolism – the presence of mobile aortic arch atheroma [8, 9].

Recently, a Mayo Clinic study including more than 200 patients with peripheral artery embolism and an equally large group of patients with AF-associated ischemic stroke helped to determine peripheral embolism's characteristic risk factors as well as differences in the clinical manifestation in comparison to cerebral artery embolization. The group of patients with peripheral thromboembolic complications was characterized by a significantly older mean age, an elevated percentage of women and individuals above 75 years of age, more frequent occurrence of symptomatic circulatory failure and an increased fraction of patients with a history of acute ischemic episode of the limbs. In contrast, patients with ischemic stroke more frequently reported a history of stroke and/or TIA. Except for prior stroke, all CHADS-2 variables were more prevalent in the group of patients with peripheral embolism. Patients with AF and peripheral embolism had a higher rate of thromboembolic recurrence [11]. Therefore the heterogeneity of the clinical course of AF-related thromboembolism may be the result of a unique subpopulation of patients with this arrhythmia.

Compared to AF-associated stroke, peripheral embolism was revealed to be associated with more frequent presence of thrombotic material in the left atrium and/or the phenomenon of SEC, reduced left ventricular ejection fraction, and higher value of the left atrial volume index in echocardiography [8, 11].

The Location of Cardiogenic Embolism

Causes of the varied location of thromboembolism in the course of AF are not definitively known. A number of factors can impact the emboli location but it is difficult to determine which of these factors play the decisive role in the distribution of thromboembolic material. In addition to the most common location, in cerebral arteries, cardiogenic emboli are usually located in extremities arteries, and most frequently in the lower limbs [12, 13]. The specific anatomical properties of the arterial system (lack of fine branching of peripheral cerebral arteries or differences in the anatomical structure of the left and right carotid and subclavian arteries) may determine the location of the embolus [7, 8]. A twice as high incidence of embolism to the right upper extremities arteries in comparison to the left side suggests that anatomical arrangement has a considerable influence on the location of an embolism. Vessel narrowings in the course of atherosclerosis and points of arterial division are at particular risk of embolization with thrombotic material [8].

AF-related thromboembolic complications can involve visceral arteries, although this is not frequently observed [6, 11, 14–17]. The embolisms of visceral arteries constitutes only several per cent of peripheral embolic complications with the upper mesenteric artery being the most frequently affected [6, 11, 16, 17]. In a Danish population study, lower and upper extremities arteries were the most frequent location of extra-cerebral thromboembolism (61% of patients). The distribution of other events were: 29% in mesenteric arteries, 9% in pelvic arteries, 7% in the aorta and 2% in the renal artery. However, the study had some limitation because the diagnosis was established on the basis of ICD-8 coding, and did not differentiate between an embolus and thrombosis as the cause of an acute arterial occlusion [7].

A higher prevalence of symptomatic embolization of carotid arteries as compared to subclavian arteries can be associated with the low-resistance and increased-volume blood flow in cerebral arteries. Furthermore, the higher prevalence of neurological deficits may be a result of the poor network of small peripheral cerebral arteries and a particular sensitivity of the nervous tissue to ischemia in comparison to others organs [8]. This hypothesis is supported by the fact that the embolization of splanchnic arteries is most commonly observed in the upper mesenteric and renal arteries which are characterized by low-resistance and high-volume blood flow [7].

Clinical Implications of Atrial Fibrillation

Atrial fibrillation is associated with higher risk of mortality, decreased quality of life and frequent hospitalization. As such, it is becoming an alarming public health issue [18]. The increased mortality associated with AF comes as a result of higher rates of heart failure and thromboembolic complications, the most common one being the stroke recorded in 80% to 90% of all embolic events [5, 8, 19, 20]. A Framingham study confirmed AF as an independent risk factor of stroke, and revealed that the risk of complications in patients with AF is five to six times higher compared to the population without this arrhythmia [20]. Ischemic stroke is the most frequent thromboembolic complication of AF and leads to serious clinical outcomes including neurological deficits, permanent impairment of cognitive function, and increased mortality. Stroke associated with AF leads to severe neurological deficits and death at a rate of 70% [21, 22]. The economic consequences of AF are also severe, due to the high costs of long-term rehabilitation

and prolonged hospitalization. AF-associated embolization of central nervous system arteries is considerably more frequent than the embolization of peripheral arteries. Consequently, the conclusions concerning AF-associated thromboembolism are based on the observation of patients with ischemic stroke. However, extra-cerebral thromboembolism in patients with AF is also associated with serious clinical consequences including the high mortality rate. A Danish population study indicated that patients with a hospital diagnosis of AF had an increased risk of peripheral thromboembolic events (relative risk, 4.0 in men and 5.7 in woman) compared to the Danish population. Extra-cerebral thromboembolism occurred in 621 (2.07%) of the 29,862 patients with AF included in the study from 1980 to 1993 [7].

Atrial Fibrillation as a Cause of Peripheral Extremities Arteries Thromboembolism

AF-related peripheral thromboembolic complications occur rarely in comparison with cerebral embolism. However, AF was diagnosed in 60–95% of patients operated on because of peripheral embolization [12, 13, 23, 24]. A number of studies dealing with the pathogenesis of peripheral emboli confirmed heart as the most frequent source of embolic material. AF is the predominant cardiologic condition associated with the formation of embolic material in the left atrium, followed by myocardial infarct. Other, less common reasons of embolization include endocarditis, valvular disorders, atrial myxoma, valvular prostheses, instable atherosclerotic plaques of the aorta, and iatrogenic causes (complications of intra-aortic balloon counterpulsation, cardioversion, coronarography, etc.) [12, 13, 23, 24]. Embolism-related limb ischemia was revealed to be associated with a higher mortality risk than the occlusion of an artery with local thrombosis in the course of atherosclerosis [12]. Furthermore, patients with AF-related peripheral embolic complications had a higher mortality risk compared to individuals with embolism associated with myocardial infarct [25].

Lorentzen et al. studied a group of 130 patients with peripheral artery embolization, and confirmed the cardiogenic origin of the embolus in 63% of the cases [12]. In this group, embolization led most commonly to acute ischemia of the lower limbs, followed by upper limb ischemia. The AF documented in 48 patients was the most frequent cause of embolization; while the myocardial infarct observed in 31 cases was the 2nd most common cause. Among the other causes were aortic

atheroma, rheumatic heart disease, atrial myxoma, and myocarditis. Additionally, it was observed that co-existing arrhythmia was associated with serious clinical implications including increased mortality, mostly due to cardiovascular complications (cause of 79% of the deaths). Ischemic heart disease, pulmonary embolism, and stroke, followed by mesenteric artery embolism, and aneurysm of the abdominal aorta were the most frequent causes of mortality. The interesting finding of the study was the fact that mitral stenosis was detected in only 1 patient [12]. This observation was particularly quaint because mitral stenosis was previously considered the most frequent cause of peripheral embolism.

Silvers et al. reported similar causes of peripheral artery embolization. Cardiologic comorbidity was confirmed in 76% of the 106 patients. Diagnosis of AF was estimated in 55% (58 people) of patients. 16 patients had a previous history of myocardial infarct, and 7 individuals had had a recent myocardial infarct. Cardiologic surgeries or cardiac catheterization were the causes of embolic complications in 13 cases. The embolization involved mostly lower limb arteries, with similar frequency at left and right extremities; 13.8% of the patients had bilateral embolic episodes. Thromboembolic complications were connected with high mortality (21.7%) during hospitalization, mainly due to cardiologic complications (17%). Other causes of mortality included renal failure, pneumonia, sepsis and pulmonary embolism. Additionally, secondary embolic episodes were observed in 34 patients (32%). Most of them occurred during the hospitalization. Cardiac disease was the cause of 76.5% (26/34) of secondary embolization, with AF being the most frequent risk factor (18/34). The risk of secondary peripheral embolization was dependant on antithrombotic therapy. The secondary thromboembolic complications developed in 40% of patients without anticoagulant therapy and in 25% of individuals on oral anticoagulation (no data if the therapy was conducted at a therapeutic level) [26].

Barreto et al. confirmed the role of AF in the pathogenesis of acute limb ischemia. They analyzed 29 cases of peripheral arterial embolism out of a total of 20,211 hospitalizations in the cardiology center. AF was documented in 68.9% of the cases (41.3% permanent and 27.5% paroxysmal AF) in their study. In opposition to Lorentzen et al.'s study, Barreto et al. indicated that most cases of permanent AF were connected with mitral stenosis, and followed by endocarditis, cardiomyopathy, and coronary artery disease. Paroxysmal AF was observed most frequent in patients with coronary artery disease and cardiomyopathy. Other reasons included valvular heart disease (most commonly

mitral stenosis and, more rarely, aortic valve insufficiency), and pulmonary hypertension. Barreto et al. confirmed that diagnosis of peripheral embolization is a poor prognostic factor. In patients with acute ischemia in the course of embolism, the mortality rate was 17.2% during a one-year follow-up. The main cause of death was recurrent thromboembolic events [23].

Summarizing, a heightened risk of cardiac morbidity and/or mortality should be anticipated in hospitalized patients with peripheral limb artery embolism. The continually increasing number of patients with AF leads to a rising demand for angiosurgical interventions due to peripheral embolism.

Atrial Fibrillation as a Cause of Organ Arterial Thrombembolism

Embolization of mesenteric, renal, or splenic arteries may be difficult to diagnose. This might be due to the frequently nonspecific or asymptomatic course of embolization in these regions, and in particular in renal arteries [7, 14–17, 27, 28]. An asymptomatic course can be the result of well-developed collateral circulation, a rich vascular network of organs with efficient compensatory mechanisms, especially if only one vessel is occluded [7, 14–17, 27, 28]. Consequently, we can expect that the prevalence of organ arterial embolization is undervalued. *Post mortem* studies support this theory [23].

Splenic Artery Embolization

Embolization of splenic vessels is a rare pathology. The prevalence of such events is difficult to determine and probably underestimated. Rich spleen vascularization, on one hand predisposed to thromboembolic episodes, on the other hand can be the reason for poorly expressed clinical manifestations. Non-specific symptoms (severe abdominal pain, nausea, vomiting) impede diagnosis [27, 28]. Diagnosis of splenic artery embolism, therefore, is determined very often on the basis of autopsy.

Atrial fibrillation is one of the most common causes of acute splenic ischemia. Hazanov et al., during a 3-year follow-up, identified 13 cases of splenic artery embolization confirmed by CT [27]. The prevalence of embolic episodes of the splenic artery amounted to 0.12%; however, the authors emphasized that this value is probably underestimated. The vascular episodes were more frequent in patients above 40 years of age. 31% (4/13) of

patients with splenic artery embolization had AF, including 3 newly diagnosed cases. Two of them had simultaneous embolic complications in other organs. Other risk factors of splenic arterial embolism included infectious endocarditis (3/13), myxomatous mitral valve (2/13), and non-infectious endocarditis in the course of malignancy (1/13) [27].

A 10-year retrospective study conducted by Antopolsky et al. indicated that AF was the most common risk factor of splenic infarction and occurred in 23% (11 persons) of 48 patients. Among the 48 individuals with splenic ischemia, 31% had hypertension, 23% diabetes mellitus, 10% previous thromboembolism, 8% previous stroke and 8% congestive heart failure, however the subgroup with AF was not analyzed separately [29]. Cardiac valvular surgery, mobile aortic atheroma, malignancy, severe liver disease, oral contraceptives, antiphospholipid syndrome, hematological diseases, mostly sickle cell anemia, myeloproliferative and lymphoproliferative disorders, and paroxysmal nocturnal hemoglobinuria are other risk factors of splenic infarction [27–29].

Renal Artery Embolization

Renal artery embolization is an uncommon condition with variable clinical presentation. There are few clinical observations, involving small groups, which concern AF as a risk factor of renal artery embolization [7, 14, 30, 31]

Korzets et al. described 11 cases of acute renal ischemia. AF occurred in 6 patients (55% of cases), and was the most common cause of thromboembolism, before ischemic heart disease and cardiomyopathy [14]. The prevalence of embolization was similar in the right and left kidney; although, previous reports have shown the more frequent occlusion of the left renal artery. An analysis of the risk factors of thromboembolism indicated that only two of the patients with AF were treated with warfarin, and both of them had non-therapeutic INR (1.6–1.8); 1 patient had activated protein C and protein S deficiency. Three individuals had earlier embolic episodes in anamnesis: acute lower limb ischemia (2 patients) and acute renal ischemia (1 patient). Diagnosis of renal artery embolization was determined during from 24 hours to 7 days from the time of admission into the hospital. Nephrolithiasis, pyelonephritis and renal cell carcinoma were considered in the differential diagnosis [14].

A retrospective study comprised of 44 patients with renal infarction and AF indicated that 14% (6 patients) had a previous embolic event. Renal embolus was diagnosed mainly in patients older

than 60 years. Lack of anticoagulation or non-therapeutic doses of warfarin were significant risks of AF-related thromboembolism; only 9 patients were treated with warfarin, and 66% of them had subtherapeutic INR. The 30-days mortality was 11.4% [30].

Rhee et al. retrospectively analyzed risk factors, comorbidities, methods of treatment and hospital mortality in 67 patients with acute renal infarct. Concurrent thromboembolic infarct (superior mesenteric artery embolism, spleen infarct, acute cerebrovascular accident, myocardial infarct) occurred in 16.4% of patients. In-hospital mortality was 8.9%, long-term mortality (follow-up 40 months) was 19.7%. Diagnosis of AF occurred in 17 cases (25.4%), and AF was the most common cause of acute renal ischemia, followed by direct vessel injury – 22.4% and hypercoagulable state (protein C, protein S deficiency, malignancy, bedridden state) – 20.9% [31].

The diagnosis of acute renal ischemia due to the embolization of the renal artery is frequently misdiagnosed or delayed, because of non-specific clinical manifestations [14, 15, 32]. Unilateral, persistent flank or abdominal pain, nausea/vomiting, fever, and elevated arterial pressure are common but non-specific symptoms. Laboratory abnormalities include haematuria, leukocytosis, and elevated LDL. Renal filtration can be normal (57.7%), mildly (16.7%), moderately (15.4%), or severely impaired (10.2%) [14, 15, 32]. Diagnosis can be estimated based on the concomitance of a condition predisposing to thromboembolic complications.

Mesenteric Artery Embolization

AF-related acute thromboembolic mesenteric ischemia has a low incidence but is connected with high mortality [32]. Acute mesenteric artery embolism usually occurs in patients above 50 years of age, with a history of cardiac diseases. Due to the progressive aging of the population, the number of incidence of mesenteric artery embolism is increasing.

Acute mesenteric ischemia most commonly results from an embolization with thrombus of cardiac origin (40–50%) and AF is considered one of the most common causes [7, 34]. Myocardial infarct, mitral stenosis, and infectious endocarditis are other important risk factors of thromboembolism of the mesenteric artery. Other reasons for acute intestinal ischemia associated with the occlusion of the mesenteric artery include local arterial thrombosis in the course of atherosclerosis or hypercoagulation state (20–30%), vascular dissection, complication of arteriography or surgical procedures. Cardiovascular comorbidities significantly worsen the forecasts of survival in this group of patients [16, 17].

The clinical spectrum of intestinal ischemia is quite extensive. Timely recognition is essential for a favorable outcome. Sudden occlusion of the mesenteric artery leads to intestinal necrosis with dramatic clinical symptoms and death. On the other hand, the clinical course in older patients with cardiologic comorbidities can be non-specific or oligosymptomatic. An asymptomatic or non-specific course of the disease can be the result of collateral

Table 1. The participation of AF in the pathogenesis of limbs and organs ischemia

Tabela 1. Udział migotania przedsionków w patogenezie niedokrwienia kończyn i narządów

Authors	Location of arteries occlusion – clinical consequences	Number of patients included to the study	Proportion of patients with AF (%)
Lorentzen et al. [12]	Limbs arteries – acute limbs ischemia	130	37
Silvers et al. [26]	Limbs arteries – acute limbs ischemia	106	55
Barreto et al. [23]	Limbs arteries – acute limbs ischemia	29	69
Hazanov et al. [27]	Splenic artery – splenic infarction	13	31
Antopolsky et al. [29]	Splenic artery – splenic infarction	48	23
Korzets et al. [14]	Renal artery – renal infarction	11	55
Hazanov et al. [30]	Renal artery – renal infarction	44	14
Rhee et al. [31]	Renal artery – renal infarction	67	25
Acosta et al. [34]	Mesenteric arteries – mesenteric ischemia	55	47

Table 2. Peripheral AF-related thromboembolism: clinical manifestations, diagnostic procedure, differential diagnosis**Tabela 2.** Zatorowość obwodowa w przebiegu MP: objawy kliniczne, badania diagnostyczne, diagnostyka różnicowa

Localization of emboli	Clinical signs and symptoms	Diagnostic procedures	Differential diagnosis
Upper/lower extremity arteries [12, 23, 24, 26]	acute limbs ischemia: an acute onset of severe pain, pulselessness, pallor, cyanosis, paresthesias, paralysis, cooling of the skin, livedo reticularis	– duplex ultrasonography – angi CT – angiography No specific laboratory findings	other causes of embolism (myocardial infarct, valvular lesion, myxoma, endocarditis, septic emboli, instable atherosclerotic plaques, aneurysm, cholesterol or atherothrombotic emboli secondary to endovascular procedures) local thrombosis (atherosclerosis, thrombosis of an arterial bypass graft, aortic/arterial dissection, aneurysm, arteritis, local spontaneous arteries thrombosis associated with a hypercoagulable state, arterial trauma, hypothermia hammer syndrome, compression of arteries (ex. popliteal artery entrapment, popliteal adventitial cyst) others: deep vein thrombosis, acute compressive neuropathy
Renal artery [13–15, 30–32]	acute, unilateral, persistent flank or abdominal pain, nausea/vomiting, fever, elevated arterial pressure	angio CT angio MR angiography renal isotope scan duplex ultrasonography laboratory tests: sometimes leukocytosis, elevated serum lactate dehydrogenase LDH, elevated creatinine level, hematuria proteinuria, impaired renal filtration	other causes of embolism (as above) local thrombosis of renal artery (atherosclerosis, thrombosis of an arterial bypass graft, aortic/arterial dissection, aneurysm, arteritis, local spontaneous arteries thrombosis associated with a hypercoagulable state, arterial trauma) renal vein thrombosis fibromuscular dysplasia nephrolithiasis, pyelonephritis, renal carcinoma others (gastritis, biliary colic, acute cholecystitis, splenic infarction, acute mesenteric ischemia)
Spleen artery [27–29]	severe left upper quadrant abdominal pain, left upper quadrant tenderness, chest pain, nausea/vomiting, constipation, fever, chills, splenomegaly; usually asymptomatic course	angio CT angio MR angiography laboratory tests: leukocytosis, elevated haematocrit, elevated serum lactate dehydrogenase level	other causes of embolism (as above) local thrombosis of spleen artery (as above) spleen vein thrombosis others (spleen abscess, acute pancreatitis, diverticulitis, nephrolithiasis, acute pyelonephritis, biliary colic, rib fracture, cirrhosis and portal hypertension)
Mesenteric artery [16, 17, 34]	severe acute abdominal pain disproportionately exaggerated relative to the unremarkable physical findings, persists beyond, fever, diarrhoea, nausea, flatulence, haematochezia, peritonitis hypotension, shock, very often nonspecific symptoms	angio CT angio MR angiography laboratory tests: leukocytosis, elevated haematocrit, metabolic acidosis, elevated serum lactate dehydrogenase level, elevated haematochezia	other causes of embolism (as above) local thrombosis of mesenteric artery (as above) fibromuscular dysplasia mesenteric and/or portal vein thrombosis mesenteric vasoconstriction (sympathetic response) others (septic shock, malignancy, pancreatitis, inflammatory bowel disease, diverticulitis, cirrhosis and portal hypotension, diabetic ketoacidosis)

circulation, previously developed due to an atherosclerotic process involving the mesenteric artery [16, 17, 34]. In most cases, mesenteric artery occlusion results in intestinal ischemia and needs immediate diagnostic imaging and surgical treatment. In older patients, diagnosis of AF, a history of recent myocardial infarct, congestive heart failure, or a history of embolic episodes should suggest the suspicion of mesenteric artery embolism [16, 17, 34].

Acute mesenteric ischemia is associated with poor prognosis, especially in patients without a history of embolism or thrombosis in splanchnic vessels [16, 17, 34].

Table 1 shows the participation of AF in the pathogenesis of limb and organ ischemia according to the studies discussed in this article. The differential diagnosis of AF-related limb and organ thromboembolism are presented in Table 2.

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Conclusions

The specific risk factors of peripheral embolism associated with AF have not been clearly identified. The results of recent studies suggest the presence of demographic, clinical, and prognostic differences between patients with peripheral thromboembolism and those with stroke. Therefore, the risk assessment of extra-cerebral embolic events, based on the CHA₂DS₂-VASc score originally developed to assess the risk of stroke, may not be optimal.

Peripheral thromboembolism is a markedly less frequent complication of AF compared to ischemic stroke; however AF should be considered an important cause of acute limb or organ ischemia with a high mortality rate. The prevalence of peripheral AF-related embolic events may be underestimated, because of a nonspecific or asymptomatic course, leading to misdiagnosis.

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