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Diagnostic challenges and emerging therapeutic strategies for aortic Thromboembolism in cats

Zahra Salehi¹, Arash Zarei^{1,*}, Sina Rouzmehr¹, Mahziyar Keshvad¹

¹ Department of Veterinary Medicine, Sho.C., Islamic Azad University, Shoushtar, Iran

ABSTRACT

Background/Objective: Aortic Thromboembolism (ATE) is a life-threatening event that can occur in cats and has a highly unpredictable outcome. This review aims to analyze the challenges related to diagnosis and to introduce innovative therapeutic strategies within the framework of this condition.

Methodology: The purpose of this systematic narrative review was to conduct a comprehensive search of the databases PubMed/Medline, Scopus, and Web of Science using relevant keywords between January 2019 and May 2024. Using a set of predetermined criteria, the eligible studies were selected, and the data were analyzed through a narrative synthesis.

Results: In conclusion, the diagnostic challenges of acute ischemic attack (ATA) include a wide range of clinical signs, from sudden hindlimb paralysis to nonspecific symptoms like shortness of breath. Additionally, current biomarkers have limitations, as seen with D-dimer's lack of specificity, which highlights the need for modern imaging techniques such as echocardiography, Doppler ultrasound, and CT angiography. Direct oral anticoagulants (DOACs), like rivaroxaban, are recognized as effective alternatives to warfarin in treatment. These DOACs have predictable pharmacokinetics, so regular monitoring isn't necessary. Clopidogrel has also demonstrated effectiveness as a first-line therapy to prevent recurrence. Conversely, aggressive treatments like thrombolysis offer limited benefits due to their high risk of side effects and low survival rates among patients.

Conclusion: Although ATE remains a significant therapeutic challenge, the combination of advanced diagnostic methods with innovative treatment approaches, especially DOACs, is promising and could lead to better clinical outcomes for cats affected by the condition. More research is needed to develop standard protocols and to evaluate clinical trials with larger sample sizes.

Keywords: Aortic thromboembolism, felines, diagnostic challenges, novel therapeutic strategies, direct oral anticoagulants, rivaroxaban.

1. INTRODUCTION

Aortic thromboembolism (ATE), commonly known as feline arterial thromboembolism (FATE) syndrome, is a painful disease and medical emergency with a guarded to poor prognosis in felines [1-3]. A thrombus, or clot, forms in the left side of the heart, usually in the left atrium or ventricle. This clot then moves down the aorta, stopping blood from flowing through the arteries [4, 5]. The most common location for a blockage to occur is at the trifurcation of the abdominal aorta, leading to acute ischemia and often paralysis of the hind limbs [6-9]. Aortic thromboembolism affects most cats who already have heart disease and are at a high risk of getting it again [10]. The pathophysiology of aortic thromboembolism is intricate and diverse; nonetheless, a definitive association with underlying cardiac disease, especially hypertrophic cardiomyopathy (HCM), is evident [2, 8, 9, 11-13]. Hemodynamic alterations and blood flow stasis in the dilated left atrium, along with subsequent hypercoagulability and platelet activation, establish a milieu favorable for thrombus formation. The presence of spontaneous echo contrast (SEC) in the left atrium and a diminished ejection fraction (EF%) are two distinct risk factors for thromboembolic events [2, 14, 15]. Recent investigations employing sophisticated echocardiography have validated these risk variables. Even though we know more about heart disease in cats, it is still hard to diagnose aortic thromboembolism. Clinical manifestations vary from typical symptoms, including abrupt hind limb paralysis, cold extremities, and absent femoral pulses, to nonspecific indicators such as respiratory distress resulting from pulmonary edema. They can also be very different from one other [14]. D-dimer levels, indicators of fibrinolysis, are frequently enhanced in acute



scenarios; nevertheless, their specificity is limited, as they may be increased in any disease associated with thrombosis and tissue necrosis [16, 17]. Consequently, a conclusive diagnosis typically depends on a synthesis of clinical evaluation, Doppler ultrasonography to ascertain blood flow disruption, and echocardiography to detect underlying cardiac pathology and thrombus formation [1]. In the past, treatment centered on thrombolysis with drugs like streptokinase and supportive care, both of which have severe side effects and low survival rates [1, 18]. But the introduction of direct oral anticoagulants (DOACs), such as rivaroxaban and apixaban, gives us new and exciting ways to stop thromboembolism from happening again [18-20]. Recent studies show that these medicines, which directly block factor Xa, have more predictable pharmacokinetics and lower the requirement for regular blood tests. Additionally, the role of antiplatelet agents such as clopidogrel in long-term therapy has garnered interest. Studies that compare clopidogrel to conventional anticoagulants like warfarin reveal that clopidogrel works better [19]. Because this disease is still a big hazard to cats, it's important to look at the current diagnostic problems and new treatments in a thorough way. The purpose of this review is to evaluate the efficacy and safety of newer medicines, including combination regimens and direct oral anticoagulants (DOACs) and to aggregate and scrutinize the most recent scientific developments in enhanced diagnostic instruments, such as innovative biomarkers and refined imaging methodologies. This initiative aims to enhance care standards and improve survival rates for cats afflicted by this life-threatening disease.

2. METHODS AND MATERIALS

This research was conducted as a narrative systematic review to provide a concise summary and critical analysis of current information on diagnostic problems and potential therapies for aortic thromboembolism in cats. To achieve this, a thorough search was performed in reputable databases such as PubMed, Scopus, Web of Science, and Google Scholar. The search used a combination of terms related to cats, aortic thromboembolism, diagnosis, therapy, and innovative technologies. Only papers published between January 1, 2019, and May 22, 2024, were included. This five-year period was chosen to highlight the most recent discoveries related to advanced diagnostic tools and current treatment approaches in feline aortic thromboembolism. After completing the search, each article was evaluated based on predefined criteria. Inclusion criteria consisted of original publications, case-control studies, case series, and clinical trials conducted in English that specifically addressed diagnostic challenges or innovative therapeutic options for aortic thromboembolism in cats. Excluded were abstracts without full texts, single case reports, brief review papers, and studies involving other species. The screening process was performed in two stages: first, screening titles and abstracts, followed by full-text review, with both stages carried out separately by two reviewers. The information from the selected articles was then organized and presented as a narrative-critical synthesis. This synthesis was divided into two main sections titled "diagnostic challenges" and "novel therapeutic approaches." Following the search and screening, a total of 25 relevant studies were included in this narrative systematic review.



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3. RESULTS

To reach a clear diagnosis from clinical symptoms, it is crucial to overcome diagnostic challenges. Diagnosing aortic thromboembolism (ATE) can be difficult because its symptoms resemble those of other diseases, and the available diagnostics are not perfect. The well-known image of a cat suddenly paralyzed with acute rear leg discomfort is common, but studies show that this is just one of several possible signs. In real life, symptoms might include difficulty breathing, extreme fatigue, loss of appetite, or even one leg going numb. These signs are not as straightforward as they seem [21-23]. Because of this, it is common for doctors to initially misdiagnose cases as trauma, poisoning, or acute respiratory distress. This can cause serious problems by preventing timely appropriate treatment. Blood biomarkers also have limitations. For instance, high levels of D-dimer are not definitive signs of acute aortic thromboembolism in cats. They mainly indicate that a clot exists but do not specify its location or cause. Elevated D-dimer levels can occur in various conditions, including pancreatitis, cancers, large abscesses, or systemic infections [24, 25].

Cardiac biomarkers such as NT-proBNP and troponin I (cTnI) help in identifying and assessing underlying heart disease, which is a major risk factor for ATE. However, these markers are not reliable for predicting thromboembolic events. For example, a cat with progressive cardiomyopathy with increased NT-proBNP and cTnI levels may never develop a thromboembolism. Conversely, diagnosing acute thromboembolism does not necessarily require proof of heart disease initially, since the main goal is to treat the thrombus and its complications [26, 27].

Ultrasound and echocardiography are key imaging tests for confirming ATE [1, 2]. Doppler ultrasonography can quickly detect absent blood flow in the arteries of the rear limbs, especially in emergencies, such as when there is no flow in the femoral or iliac arteries. Echocardiography is primarily used to examine heart conditions like hypertrophic cardiomyopathy and to locate the clot in the left atrium. The presence of "spontaneous echo contrast" (SEC), which appears as smoke in the left atrium, indicates a higher risk of clot formation [28, 29]. CT angiography provides the most detailed view of the clot, including its size and location. However, because cats require general anesthesia for this procedure—something that can be risky in unstable patients it is not performed frequently [29]. Emergency care, limiting clot expansion, and preventing recurrence are key aspects of ATE management. Significant progress has been made in this area [30].

Warfarin's traditional use was complicated by side effects such as bleeding and frequent blood monitoring. Rivaroxaban has emerged as a promising oral anticoagulant that directly inhibits factor Xa, a critical component of clot formation. Studies indicate that rivaroxaban is more effective in cats because it provides continuous anticoagulation with fewer blood tests. Doses of 0.5 to 1 mg/kg every 12 hours have shown efficacy in preventing recurrent thromboembolism [1, 19, 31].

Clinical research shows clopidogrel is superior to aspirin at preventing recurrent thromboembolism when given at 75 mg daily. It is now the recommended treatment for most at-risk cats. Recent studies comparing combinations of clopidogrel and aspirin, without warfarin, suggest similar survival outcomes with fewer side effects [1, 19, 31, 32].

Thrombolysis involves medications like streptokinase or alteplase to dissolve clots. Although theoretically ideal, its use is limited by the high risk of severe bleeding and low survival rates less than 40% in most studies. Therefore, it's reserved for specific cases after careful benefit-risk assessment [18]. Mechanical thrombectomy, the removal of clots via a catheter, has been reported but is not yet common in treating feline ATE due to the need for specialized staff and equipment. This approach remains experimental despite some notable successes [33, 34].

4. DISCUSSION

Feline aortic thromboembolism continues to present a multifaceted issue characterized by various diagnostic and treatment difficulties. The results of this systematic review, which examines publications from the past five years (2019–2024), reveal that while much progress has been achieved in comprehending the pathogenesis and treatment of this condition, numerous knowledge deficits persist.



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Research indicates that depending exclusively on the traditional presentation of hindlimb paralysis may result in misinterpretation or delayed diagnosis. Widyaputri et al. (2024) conducted a study involving 21 cats, revealing that up to 30% of cases may exhibit nonspecific indications, including dyspnea or pronounced lethargy. This underscores the necessity of including ATE in the differential diagnosis for any cat with acute respiratory symptoms or generalized weakness [35].

it is not very specific [36]. This biomarker is elevated in many illnesses linked to systemic inflammation and tissue necrosis. Conversely, the integration of cardiac biomarkers (NT-proBNP and cTnI) with echocardiography is regarded as the most thorough diagnostic methodology. Rush et al. (2020) demonstrated that the existence of "spontaneous echo contrast" (SEC) in the left atrium serves as a robust and independent predictor of thromboembolism risk [26].

The most significant advancement in the management of ATE has been the introduction of direct oral anticoagulants (DOACs). Lo et al. (2022) conducted studies on rivaroxaban, demonstrating that it possesses comparable efficacy to conventional regimens while substantially alleviating the treatment burden for animal owners by negating the necessity for frequent laboratory monitoring [19]. This quality makes DOACs an excellent choice for long-term relapse prevention. Simultaneously, the significance of clopidogrel as a fundamental component of antiplatelet treatment has been affirmed. A research by Guillaumin et al. (2024) that looked at numerous antithrombotic regimens found that the combination of clopidogrel and aspirin, without warfarin, was the safest and most effective [1]. This discovery has prompted a therapeutic strategy aimed at streamlining regimens and mitigating adverse effects. The scientific consensus on invasive therapy is predicated on the intrinsic limits of thrombolysis. Welsh et al. (2022) examined dose-adjusted procedures; however, the incidence of severe adverse events, including lethal hemorrhage, has been reported as elevated [17]. Mechanical thrombectomy, despite its efficacy in case reports, remains unavailable in practice due to the requirement for advanced and specialized equipment [37].

The primary constraint in the domain of ATE is the absence of randomized clinical trial trials with adequate sample size. The majority of the existing information derives from retrospective research, case series, or isolated accounts. This has made it hard to develop standardized treatment plans based on evidence.

Future directions should encompass:

1. Planning future multicenter studies to directly evaluate the safety and effectiveness of DOACs with combination regimens.
2. Finding and confirming new biomarkers that can help us better predict the likelihood of blood clots forming.
3. Creating a set of rules for both short-term and long-term care based on each patient's risk level.

5. CONCLUSION

The diagnostic and therapeutic challenges of feline aortic thromboembolism remain significant issues in veterinary medicine. Nevertheless, this narrative systematic review shows that despite the challenges ahead, the outlook for the management of aortic thromboembolism in cats is promising. Although many clinical signs and limited biomarkers make quick and accurate diagnosis difficult, advanced imaging techniques such as echocardiography and Doppler ultrasound are becoming increasingly crucial for precise identification. The development of new anticoagulants like rivaroxaban has transformed treatment by making preventive strategies more predictable and reducing the need for frequent monitoring. Clopidogrel, on the other hand, has become a key component of antithrombotic therapy, commonly used as a first-line option to decrease platelet aggregation. Conversely, invasive treatments like thrombolysis are reserved for specific cases due to their considerable risks. With these advances, future management of this condition is likely to focus on three main areas: 1. Developing and standardizing faster, less invasive diagnostic methods 2. Conducting more clinical trials to ensure the safety and efficacy of new medications 3. Creating evidence-based, integrated protocols for comprehensive patient care, from diagnosis to recurrence prevention. Ultimately, aortic thromboembolism remains a life-threatening disease, but combining improved diagnostic tools with innovative treatments could not only increase survival rates but also substantially enhance patients' quality of life.



Declarations and statements

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Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

All applicable international, national, and/or institutional guidelines for writing a review paper were followed.

Author contribution

Conceptualization: [Zahra Salehi], ...; Methodology: [All Authors], ...; Formal analysis and investigation: [All Authors], ...; Writing - original draft preparation: [All Authors]; Writing - review and editing: [Arash Zarei], ...; Funding acquisition: [Self-funding], ...; Supervision: [Zahra Salehi].

Consent to participate

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Declaration of the use of generative AI

Not used.

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