



# Clinical Utility of [<sup>18</sup>F]FDG-PET /CT in Pericardial Disease

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## Abstract

Identification of the etiology of pericardial disease is challenging because the accessibility to pericardial fluid and tissue is limited and there is a relatively low yield of fluid and tissue analysis. Pericardial disease is associated with various systemic diseases and is frequently a first manifestation of other systemic diseases. Detecting the cause of pericarditis and minimizing the subsequent inflammatory process can possibly prevent long-term complications.

**Purpose of Review** To review the clinical utility of [<sup>18</sup>F]-2-deoxy-2-fluoro-D-glucose positron emission tomography/computed tomography ([<sup>18</sup>F]FDG-PET/CT) in the diagnosis and treatment of pericardial disease.

**Recent Findings** [<sup>18</sup>F]FDG-PET/CT can visualize the hypermetabolic tissues of both malignancy and inflammation. Distribution of [<sup>18</sup>F]FDG-PET/CT uptake can provide information for neoplastic disease. If malignancy is ruled out, high uptake of pericardium is associated with active inflammation of the pericardium, and thus response to anti-inflammatory agents can also be predicted with [<sup>18</sup>F]FDG-PET/CT imaging.

**Summary** [<sup>18</sup>F]FDG-PET/CT can be helpful for diagnosing and establishing prognosis and for planning for anti-inflammatory treatment in pericardial disease.

**Keywords** Positron emission tomography · Pericardial disease · Pericarditis · Constrictive pericarditis

## Introduction

Pericardial disease is frequently associated with systemic disease and the treatment plan and prognosis depends on the underlying disease. The etiology of pericardial disease can be categorized [1] (Table 1) as infectious versus noninfectious and malignant versus nonmalignant. Since there are so many etiologies resulting in pericardial diseases with similar clinical manifestations, it is often difficult to find out the differential etiologic diagnosis of pericardial disease. Moreover, the identification of

the underlying etiology is challenging because assessment to pericardial effusion is limited, and even after pericardial fluid analysis, it does not always give an answer and assessment is limited especially in effusive-constrictive or constrictive pericarditis. Even after biopsy of pericardium, diagnostic yield is low.

[<sup>18</sup>F]-2-deoxy-2-fluoro-D-glucose positron emission tomography ([<sup>18</sup>F]FDG-PET/CT) is an imaging biomarker of glucose metabolism, and increased glucose metabolism is a hallmark of inflammation or malignancy [2]. Although [<sup>18</sup>F]FDG-PET/CT is commonly used in oncology fields, it can also visualize the inflammation. Etiology of pericardial disease includes infectious, neoplastic, autoimmune, metabolic, iatrogenic, and traumatic causes. A noninflammatory cause from chronic heart failure, pulmonary arterial hypertension, aortic dissection, amyloidosis should also be considered. Therefore, differential diagnosis of pericardial disease is always based on the clinical history, including the symptoms and signs and additional diagnostic testing, to decide whether it is an inflammatory condition or not. Systemic inflammatory markers including C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) is helpful for detecting the inflammatory disease; however, it does not always suggest inflammation of pericardium. Transechocardiography (TTE) is an excellent modality to diagnosis clinical syndrome of

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**Table 1** Etiology of pericardial disease

A. Infectious causes	Viral (common) Bacterial Fungal (very rare) Parasitic (very rare)
B. Noninfectious cause	<u>Autoimmune</u> <u>Neoplastic : primary tumors (rare), metastatic tumors (common, lung, breast, and lymphoma is the most common)</u> Metabolic : <u>uremia</u> , myxedema, anorexia nervosa, others rare Traumatic or iatrogenic: - Early onset (rare): direct or indirect injury - <u>Late onset (common): postmyocardial infarction syndrome, postpericardiotomy syndrome, posttraumatic including iatrogenic trauma (e.g., coronary intervention, pacemaker lead insertion and radiofrequency ablation)</u> <u>Drug-related: rare</u> Other (common): amyloidosis, aortic dissection, pulmonary arterial hypertension, and chronic heart failure Other (uncommon) congenital partial and complete absence of the pericardium

\*Underlying means possibly inflammatory pericardial disease

(From: Adler Y, et al. European Heart Journal. 2015;36(42):2921-64, by permission of Oxford University Press) [1]

pericardial disease, e.g., pericardial effusion, constrictive pericarditis, effusive-constrictive pericarditis, and cardiac tamponade; however, it only gives morphologic and hemodynamic data and is limited in visualizing the inflammation. Cardiac MRI also has limited use or is contraindicated in renal failure, claustrophobia, or pacemakers. In this review, we summarized how [ $^{18}\text{F}$ ]FDG-PET/CT works in each disease category and the utility of [ $^{18}\text{F}$ ]FDG-PET/CT in treatment and follow-up.

## [ $^{18}\text{F}$ ]FDG-PET/CT in Neoplastic Pericardial Disease

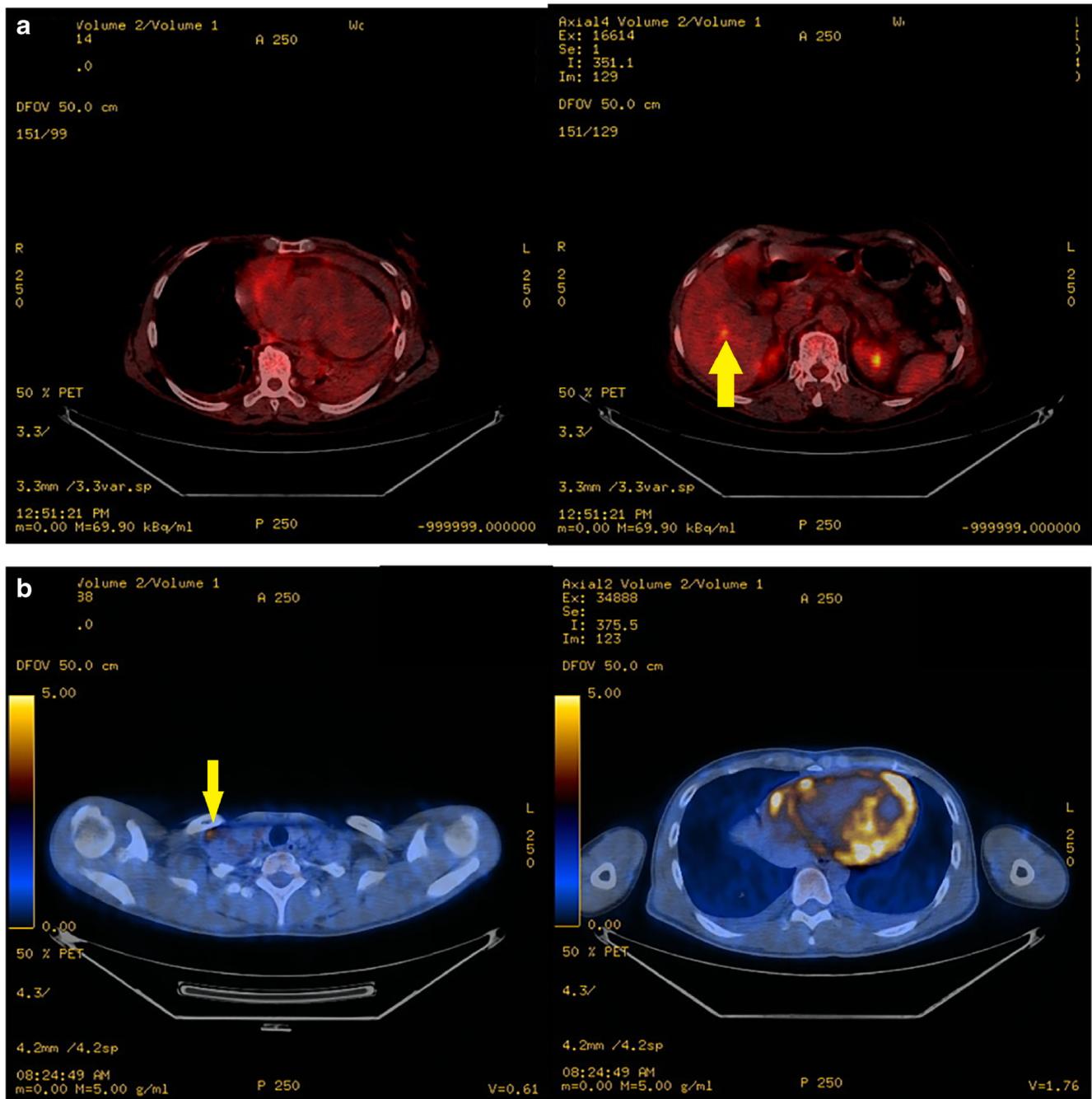
Pericardial disease in neoplastic disease can be primary involvement of the disease itself (metastatic or primary pericardial malignancy) or secondary involvement of the disease, including paraneoplastic syndrome. The most common malignant diseases associated with metastatic pericardial effusion are breast and lung cancer and Hodgkin lymphoma. The primary tumor in pericardium manifesting as a pericardial effusion is mesothelioma [3]. Sarcoma and lymphoma also can be presented as pericardial effusion or constrictive pericarditis.

In patients who have no previous history of malignancy, previous study [4] from an unselected pericarditis cohort reported that up to 5% of cases are attributed to cancer pathogenesis. The ratio of malignancy increases between 12% and 23% when the pericarditis is accompanied with pericardial effusion [5, 6]. A recent study by Sogaard et al. reported [7] that patients with newly diagnosed pericarditis had higher

risks than age- and sex-matched members of the general population of being diagnosed with lung cancer, non-Hodgkin lymphoma, and myeloid leukemia during the first 3 months after a pericarditis diagnosis. Surprisingly, the increased risk for lung cancer, non-Hodgkin lymphoma, and bladder cancer persisted even beyond 1 year after a pericarditis diagnosis. Therefore, detecting underlying malignancy in pericardial disease should be considered especially in patients with pericarditis and pericardial effusion.

[ $^{18}\text{F}$ ]FDG-PET/CT in neoplastic disease reveals high standardized uptake value (SUV) in neoplasm, and therefore it can visualize the origin of neoplasm if the pericardial disease is associated with neoplastic disease, because the diagnostic yield of pericardial biopsy is unsatisfactory [8]. Although cytology is superior to pericardial biopsy in diagnosing metastatic carcinoma, cytology is not always available and other tumors may go undetected in the pericardial effusion [9]. In undetected but suspected cases, pathologic assessment in other solid lesion gives better results for diagnosis and single examination of a whole body [ $^{18}\text{F}$ ]FDG-PET/CT scan is helpful to find other malignant lesions (Fig. 1a).

During staging of the malignancy, the presence of a malignant pericardial effusion changes the stage to advanced stage, which results in critical changes in the treatment plan. The problem is that pericardial effusion can be associated with general conditions, such as hypoalbuminemia or anemia. In the case of malignant effusion, adjacent lymph node metastasis is combined and it can be assessed with a single exam of [ $^{18}\text{F}$ ]FDG-PET/CT. High [ $^{18}\text{F}$ ]FDG uptake in mediastinal or other adjacent lymph nodes can be found, and the extent and



**Fig. 1.** **a** A 56-year-old woman with dyspnea and pericardial effusion. Pericardiocentesis was done and cytology did not prove the evidence of malignancy and chronic active inflammation with fibrosis was reported from pericardial biopsy. However,  $^{18}\text{F}$ FDG-PET revealed the hepatic uptake and liver biopsy revealed malignant hemangioendothelioma (yellow arrow). **b** A 20-year-old young man visited our hospital with chest pain and dyspnea. Echocardiography demonstrated thickened

pericardium with constrictive physiology. Pericardial biopsy was planned, and  $^{18}\text{F}$ FDG-PET was performed to confirm the biopsy site and extent of disease. Supraclavicular lymph node uptake was confirmed, and gun-biopsy was performed before pericardial biopsy. AFB staining was positive and he was diagnosed as pericardial tuberculosis with tuberculous lymphadenitis (yellow arrow)

distribution of positive uptake can be suggestive for malignancy or benign infectious disease [10]. However, differentiation between benign and malignant pericardial disease, as well as differentiation between physiological and pathological [ $^{18}\text{F}$ ]FDG-PET/CT, remains challenging.

### [ $^{18}\text{F}$ ]FDG-PET/CT in Infectious Pericardial Disease

Infectious pericardial diseases include viral, bacterial, fungal, and rarely parasitic. Viral pericarditis is the most common type

of acute pericarditis and is usually not so severe and self-limiting and rarely progresses to cardiac tamponade [11]. Clinically, it mimics idiopathic pericarditis. Diagnosis of viral pericarditis assumed by clinical history and specific viral exam is not confirmed in most cases. Although viral pericarditis is a mild disease in most cases, the presence of combined myocarditis (myopericarditis) is high risk for heart failure and poor prognosis [12]. Elevation of cardiac enzymes (troponin) is a sensitive marker for myocarditis and confirmative diagnosis is cardiac biopsy. Involvement of myocardium can be visualized by imaging study with cardiac magnetic resonance imaging (MRI) [13]. [<sup>18</sup>F]FDG-PET/CT can also visualize the myocardial inflammation and have a good correlation with cardiac MRI [14].

Bacterial and fungal pericarditis is rare in the modern era, whereas it is more common in immunocompromised patients and accompanied adjacent organs. Rapid progression and septic shock is common and pericardial effusion is purulent. Therefore, echocardiography and computed tomography are more helpful in the diagnosis of viral, bacterial, and fungal pericarditis than [<sup>18</sup>F]FDG-PET/CT with rapid assessment and decision making. However, [<sup>18</sup>F]FDG-PET/CT can be helpful in selective cases combined with disseminated infections, such as infective endocarditis [15]. Riet et al enrolled 24 patients with 25 episodes of endocarditis, and they underwent [<sup>18</sup>F]FDG-PET/CT to detect and localize peripheral embolism or distant infection. Peripheral embolization and/or metastatic infection in 11 episodes (44%) was demonstrated in [<sup>18</sup>F]FDG-PET/CT. Among them, one episode had a positive lesion for both embolism and metastatic infection. [<sup>18</sup>F]FDG-PET/CT detected seven positive cases (28%) in which there was no clinical suspicion. Valve involvement of endocarditis was seen only in three patients (12%). Detecting metastatic infection and septic embolization is helpful to decide the duration of antibiotics therapy and decision for surgical drainage.

The most troublesome etiology of infectious pericarditis is tuberculous pericarditis because clinical manifestation of tuberculous pericarditis is variable from the asymptomatic state to cardiac tamponade, or constrictive pericarditis and diagnostic yield of pericardial biopsy or AFB staining is poor. In the case of pericardial effusion, detection rate of a direct smear of AFB is variable from 0–42% [16, 17]. An AFB culture can increase the diagnostic yield; however, it requires more than 6 weeks, which is too late for patient's management. Untreated tuberculous pericarditis has high morbidity and mortality and frequently results in constrictive pericarditis [17], which requires surgical treatment with poorer long term outcomes. Therefore, diagnosis is made on a multifactorial analysis of clinical, imaging, chemical, and bacteriological and serological basis. TTE for tuberculous pericarditis can be helpful to assess the clinical syndrome of pericardial disease to decide the pericardiocentesis or heart failure management combined with constrictive pericarditis; however, it is not diagnostic for

pericardial tuberculosis. Tuberculous pericarditis is frequently associated with pulmonary tuberculosis or lymph node involvement. [<sup>18</sup>F]FDG-PET/CT is superior to CT in detecting extrapulmonary tuberculosis. Dual phase [<sup>18</sup>F]FDG-PET/CT versus a routine staging study by Sthekge et al. [18] reported that 18 sites of lymph node in nine patients were identified on both early and delayed images. Nine out of 18 sites were not detected in CT. In this study, tuberculoma had high SUVmax (standardized uptake value) (mean 11.02). Dong et al. also reported in a retrospective review that differential diagnosis of acute tuberculous pericarditis and idiopathic pericarditis is possible using [<sup>18</sup>F]FDG-PET/CT [19]. The authors also used SUVmax of mediastinal clavicular and supraclavicular lymph nodes, and it was significantly higher in tuberculous pericarditis. The pattern of lymph node uptake can be used to diagnosis tuberculous pericarditis. Furthermore, [<sup>18</sup>F]FDG-PET/CT is helpful for identification of pulmonary and other organ involvement in tuberculosis, staging of tuberculosis, and assessment of treatment response [20]. A representative case (Fig. 1b) shows multiple organ involvement, including lymph node and pericardium. This patient was presented as constrictive pericarditis with bilateral pleural effusion and pleural effusion was not diagnostic and there was no pericardial effusion. During planning for pericardial biopsy, [<sup>18</sup>F]FDG-PET/CT was performed and high SUV in right supraclavicular lymph node was observed. Percutaneous needle biopsy was done, and it revealed caseous necrosis and positive AFB staining. Pericardial biopsy was canceled consequently, and he was treated successfully with anti-tuberculosis medication and steroids.

### [<sup>18</sup>F]FDG-PET/CT in Constrictive Pericarditis

Constrictive pericarditis is a unique pericardial syndrome that presents as heart failure [21]. Because of the chronic inflammatory process of pericardium, thickening of pericardium progresses and isolation of pericardial pressure from intrathoracic pressure results in ventricular interdependency, and it is a hallmark of constrictive physiology. Pericardial adhesion to epicardium limits the longitudinal motion of myocardium and finally results in left and/or right ventricular failure. Classically, constrictive pericarditis was thought to be an irreversible chronic inflammation of the pericardium, and therefore it was considered as a surgical disease [22]; however, assessment of hemodynamics by serial echocardiography [23] reveals that constrictive physiology occurs during acute or subacute inflammation of the pericardium [24, 25].

Transient constrictive pericarditis has been reported in various underlying etiologies with or without anti-inflammatory treatment [26, 27]. The etiology of transient constrictive pericarditis is variable, including idiopathic, postsurgical,

associated with connective tissue disease, or infection. Spontaneous regression of inflammation has also been reported; however, progression of pericarditis from pericarditis with effusion to effusive-constrictive pericarditis even with nonsteroidal anti-inflammatory drugs or colchicine observed in clinical practice and strong anti-inflammatory therapy with steroids can theoretically rescue the patients in early inflammatory phases with optimal management for underlying diseases. However, in clinical practice, it is not easy to decide whether constrictive pericarditis is reversible or not. Presentation of symptoms is often insidious, and duration of symptoms does not reflect the irreversibility. Inflammatory markers in blood tests can suggest the active inflammation in pericardium; however, sensitivity is low because the burden of pericardial inflammation to systemic inflammation is relatively low with low sensitivity and specificity [28]. Therefore, if there is an absence of definite evidence for chronic inflammation, such as pericardial calcification or liver cirrhosis associated with chronic congestion, the possibility to respond to medical treatment should always be considered. Current guidelines recommend that empiric anti-inflammatory therapy may be considered in cases with transient or a new diagnosis of constriction with concomitant evidence of pericardial inflammation, including CRP/ESR elevation or pericardial enhancement on CT/CMR.

[<sup>18</sup>F]FDG-PET/CT is excellent for visualization of pericardium with high sensitivity, and a prospective study was recently performed by Chang et al. [29••]. In this study, 16 patients who were diagnosed as constrictive pericarditis were included. Exclusion criteria were pericardial calcification, history of malignancy, radiation therapy, and rapid improvement of CP within 1 week with ibuprofen/colchicine therapy. [<sup>18</sup>F]FDG-PET/CT was performed at enrollment and a follow-up scan was acquired after 3 months of steroid therapy. Treatment response was categorized as follows: nonresponders, responder, and partial responders. Partial responders were defined as steroid-dependent CP patients whose symptom/signs had improved during the early phase of treatment but were aggravated during steroid tapering and were eventually grouped as nonresponders. There were nine responders (56%) and seven nonresponders (44%). Pericardial SUVmax was >3.0 in all responders, whereas no patients with a pericardial SUVmax <3.0 responded to steroid therapy. Two nonresponders with a pericardial SUVmax >3.0 were partial responders who finally remained as nonresponder. High SUV in pericardium at baseline studies decreased after 3 months of steroid therapy. Using a pericardial SUVmax of 3.0 as a cutoff value, the sensitivity, specificity, positive predictive, and negative predictive values of [<sup>18</sup>F]FDG PET/CT for predicting responders were 100%, 71%, 82%, and 100%, respectively. This study suggests that the presence of pericardial inflammation is a key role of

reversibility of transient constrictive pericarditis and [<sup>18</sup>F]FDG PET/CT visualizes it with high sensitivity and specificity.

### Optimizing Patients Preparation for [<sup>18</sup>F]FDG-PET Protocol in Pericardial Disease

Glucose uptake is increased in the myocardium in normal subjects, and therefore interpretation of glucose uptake in the pericardium can be confused when normal glucose uptake for the myocardium is not suppressed. Furthermore, myocardial disease also produces pericardial effusion; thus, preparation for optimal imaging gives better outcome in utility of [<sup>18</sup>F]FDG-PET in pericardial and combined myocardial diseases. Recommended patients preparation for [<sup>18</sup>F]FDG-PET in myocardial and pericardial diseases is as follows [30]: prolonged fast, high-fat/low-carbohydrate diet, iv unfractionated heparin, and a combination of these methods.

In detail, the primary dietary preparation with avoidance of carbohydrate-containing foods should begin about 24 hours prior to the test, with an intake of high-fat and high-protein foods for at least two meals 24 hours prior, and then an overnight fasting should be recommended. There should be awareness about the administration of glucose-containing intravenous medications and uncommon activity resulting in glucose uptake, such as peritoneal dialysis. Suppression of myocyte glucose uptake can be achieved by giving iv unfractionated heparin (15–50 units of regular intravenous heparin 15 min prior to intravenous [<sup>18</sup>F]FDG administration or 500 IU of intravenous heparin 45 min and 15 min (total 1000 IU) prior to intravenous IV [<sup>18</sup>F]FDG) [31], which results in elevated plasma levels of free fatty acids and increasing cardiac utilization of free fatty acids instead of glucose, without increasing partial thromboplastin time.

### Conclusions

[<sup>18</sup>F]FDG-PET is helpful in diagnosis and treatment of pericardial disease in aspects of 1) presumptive diagnosis of malignancy, especially in nondiagnostic pericardial effusion or technically risky for pericardiocentesis, 2) selection of optimal biopsy site with high yield of disease, 3) metastatic infection in purulent pericarditis with septicemia, 4) extent of tuberculosis pericarditis and possibly additional information for diagnosis of tuberculous pericarditis, and 5) detecting reversible, transient pericarditis with high sensitivity. Further clinical investigation for utility of [<sup>18</sup>F]FDG-PET will give more evidence for extended clinical utility.

## Compliance with Ethical Standards

**Conflict of Interest** Min-Sun Kim, Eun-Kyung Kim, Joon Young Choi, Jae K. Oh, and Sung-A Chang declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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