

## Cardiac implications in myasthenia gravis

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### Abstract

This editorial aimed to consolidate the current evidence in literature on the association between myasthenia gravis (MG) and cardiac involvement, focusing on the impact of thymoma, antistriational antibodies, and late-onset MG. Additionally, the study aimed to explore the influence of genetic differences among populations on the association with cardiac disease. We conducted a review of existing literature in PubMed and Google Scholar to find relevant studies on cardiac involvement in MG. We created search criteria using a combination of free text words, including MG, antistriational antibodies, thymectomy, cardiomyopathy, myocarditis, arrhythmias, autonomic dysfunction. Relevant articles published in English language were analyzed and incorporated. The findings indicate a strong association between thymoma, myasthenic crisis, antistriational antibodies, and late-onset MG with cardiac involvement. The study also revealed that genetic differences among populations influence the risk of cardiac disease and electrocardiography (ECG) abnormalities in MG patients. Autonomic dysfunctions altered cardiac autonomic response and increased susceptibility to arrhythmias and sudden cardiac death in MG patients. The study supports the significance of thymoma, antistriational antibodies, and late-onset MG as key factors associated with cardiac involvement in MG patients. It emphasizes the importance of ECG as the initial test in managing MG patients, particularly in the perioperative period, to identify and genetic testing if needed to address their cardiac risk effectively.

**Key Words:** Myasthenia gravis; Antistriational antibodies; Thymectomy; Cardiomyopathy; Myocarditis; Arrhythmias; Autonomic dysfunction

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**Core Tip:** Preoperative cardiac screening is crucial for patients with myasthenia gravis (MG), especially those with thymoma, late-onset MG, or antistriational antibodies. Understanding the link between MG and cardiac conditions such as cardiomyopathy, myocarditis, takotsubo cardiomyopathy, autonomic dysfunction, and arrhythmias is essential for perioperative surgical management. Electrocardiography and Troponin T can be important initial screening tests in patients with high risk suspicion. Comprehensive screening protocols are necessary to mitigate cardiac risks and optimize outcomes in MG patients undergoing surgery.

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## INTRODUCTION

Myasthenia gravis (MG) is a disorder that affects the skeletal and cardiac muscles. Patients have autoantibodies against the Acetylcholine receptor, muscle-specific tyrosine kinase, and low-density lipoprotein receptor-related protein four. Based on the literature, the incidence of MG is 4.1 to 30 per 100000, and prevalence is 150-to 200 per 100000[1]. The exact cardiac prevalence of MG is unknown in current literature. In the presence of thymoma the prevalence can range from 10%-15%[2]. Patients post thymectomy had decreased cardiac involvement[3]. Perioperative considerations in MG patients are related to cardiorespiratory manifestations and myasthenic crisis. MG patients can also have antistriational autoantibodies, including anti-titin, ryanodine receptor, anti-muscular voltage-gated potassium channel (Kv1.4), and myositis-specific antibodies. Antistriational exists because of their binding in a cross-striation pattern to skeletal and heart muscle tissue sections.

Romi *et al*[4] in their study of Caucasian patients with MG, found that patients with anti Kv1.4 antibodies had late onset and mild MG, which is in contrast to Japanese patients with similar antibodies who had severe MG symptoms, including thymoma, myasthenic crisis, myocarditis, and QT prolongation[4-6]. This could be due to other contributing factors, including genetic differences in this population, and thus, disease severity may not be related to anti-Kv1.4 antibodies alone. Perioperative cardiac testing in MG patients ensures the identification of cardiac issues that can be effectively managed in the operative period. In this editorial, we discuss Nag *et al*[7] manuscript on perioperative cardiac risks in MG patients.

## INCREASED CARDIAC RISK IN MG PATIENTS

Heart and skeletal muscle are proposed autoimmune targets for MG patients. Evidence in the literature reports the association of antistriational autoantibodies with cardiac manifestations. Anti-titin antibodies have also been reported to be associated with thymoma-associated MG[8,9]. The clarity regarding the frequency and intensity of the association remains uncertain. Nag *et al*[7] do not provide information on cardiac screening tests in MG patients and algorithms for screening considerations. Patients with myasthenic crisis and underlying cardiac disease, including hypertensive cardiomyopathy, atrial fibrillation, and ischemic heart disease, had an increased risk of non-invasive ventilation failure on attempting weaning from mechanical ventilation[10]. In a study by Kato *et al*[11] on MG patients, the authors found electrocardiography (ECG) as the best initial step for screening MG to assess patients for cardiac risk. Common ECG abnormalities observed were persistent atrial fibrillation, atrioventricular block, ST segment depression and negative T waves, early repolarization, left ventricular hypertrophy, and prolonged QTc interval[11,12]. Echocardiography should be considered as the next step if abnormalities are noted in ECG or in patients presenting with heart failure, arrhythmias, or signs of myocarditis[11]. Kato *et al*[11] and Tsugawa *et al*[12] described that around 56%-62% have ECG abnormalities in MG patients, particularly those not on immunosuppressant therapy. In a study by Furlund Owe *et al*[13] on MG patients compared to healthy controls on echocardiography, left ventricular systolic and diastolic function did not differ between the groups. This further strengthens the recommendation to consider ECG as the screening step to identify cardiac involvement in MG patients. For symptomatic patients with dyspnea, chest pain, and ECG changes or ECHO abnormalities, troponin levels can also be considered. Elevated cardiac troponins also mean that the patients' MG is not well controlled, and treatment with immunosuppressive therapy is required[14]. The cardiopulmonary function can be tested using the 6-minute walk distance in MG patients with poor functional status since low walk distance was associated with longer hospital stays after thymectomy[15,16].

## CARDIOMYOPATHY, MYOCARDITIS IN MG

MG has been associated with dilated cardiomyopathy (DCM) based on prior studies by Zhou *et al*[17] on genetic analysis. The authors state midline 1 interacting protein 1 and PI3K-interacting protein 1 in MG-associated DCM[17]. Myocarditis,

thymoma, and late-onset MG were associated with antistriational antibodies on a flow cytometry analysis of patient samples over 13 years in a study by Kufukihara *et al*[18]. All myocarditis patients had at least one of these autoantibodies, and 70% had thymoma. Suzuki *et al*[6] report that out of 924 patients with MG, three patients developed myocarditis and seven patients had at least one Antistriational antibody positive, and four had thymoma. Nag *et al*[7] state also state that the presence of thymoma increases the risk of cardiac complications in MG patients to 10%-15% based on current literature. In a study of 247 patients with MG, the presence of anti-titin antibodies was associated with myocarditis in 17 of 25 patients. The authors also reported that anti-titin antibodies and Myasthenic crisis were associated with myocarditis, but no association was found with thymoma[19]. Thus, there is strong literature on the association of antistriational antibodies in association with myocarditis. However, the association of thymoma with myocarditis is still conflicted. Cheng *et al*[20] in their systematic review on myocarditis in MG patients state dyspnea as the commonest presentation and reports a 50% hospital mortality rate in these patients.

Chen *et al*[21] on their retrospective study of hospitalized patients with MG found increasing age, presence of infection, immune checkpoint inhibitors therapy and ongoing myasthenic crisis, and thymoma were associated with elevated troponin T levels (> 14 ng/L). High troponins, female sex, thymoma and infection were a predictor of death in hospitalization. This measuring biomarkers in hospitalized patients with MG may be beneficial. Patients with autoimmune disease, particularly MG, are at increased risk for Takotsubo cardiomyopathy (TCM) based on multiple pieces of evidence in the literature and are often mistaken for acute coronary syndrome. Farjoud Kouhanjani *et al*[22] describe 18.8% of patients with autoimmune disease had TCM. The EKG findings in TCM commonly include normal EKG, T wave inversions, ST segment elevations, prolongation of the QT interval, and transient q waves. Nag *et al*[7] describe TCM in MG, particularly those with myasthenic crisis. Rathish and Karalliyadda[23] performed a systematic review of TCM in MG patients and found that all patients were in myasthenic crisis at presentation. They also document that half the patients had no prior diagnosis of MG prior to presentation.

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## CARDIAC ARRHYTHMIAS IN MG

Nag *et al*[7] describe arrhythmia, sick sinus syndrome, and heart block in MG patients. Gandhi *et al*[3] in their retrospective study on MG for 10 years found the prevalence of cardiac arrhythmias to be around 17%. The authors also state patients with thymectomy had less cardiac involvement suggesting that thymoma was associated with higher cardiac risk [3]. Evidence in the literature also reports MG patients with severe bradycardia with positive anti-striation antibodies, anti-muscular voltage-gated potassium channel-complex (Kv1.4) antibodies, and anti-titin antibodies[24].

Multiple pieces of evidence in the literature report atrial fibrillation in myasthenic crisis patients. These patients often had acetylcholinesterase receptor antibody positive[25].

The authors fail to mention in detail the autonomic functions that are altered in MG patients, including cardiac autonomic response, sympathetic and parasympathetic dysfunction, particularly during periods of hemodynamic instability, lower sensitivity of baroreflexes, and higher sympathetic and vagal balance at rest, and orthostatic alterations[26-28]. These authors found abnormalities in cardiovascular reflex testing; heart rate variability was assessed using a 20-minute ECG recording, 24-hour ECG monitoring, Valsalva maneuver, and orthostasis. These autonomic dysfunctions can predispose patients with MG to develop arrhythmias and sudden cardiac death[28,29]. Arrhythmic episodes are often noted during periods of stress and surgery, including thymectomy[30].

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## FUTURE RECOMMENDATIONS

Future studies should focus on antibody and genetic testing in MG patients to apply precision medicine in managing patients in the perioperative period and in assessing their cumulative cardiac risk. There is an increased need for more pathological testing to confirm the cardiac risks associated with MG. This will provide a clear direction for future research and aid in early diagnosis of cardiac involvement.

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## CONCLUSION

We agree with the authors Nag *et al*[7] that thymoma, antistriational antibodies, and late onset MG are associated with cardiac involvement. Genetic differences and thymoma among populations also tend to influence the association with cardiac disease, ECG abnormalities and troponin T levels. The presence of thymoma, myasthenic crisis, and antistriational antibodies appears to have a stronger risk for cardiac involvement. ECG serves as the best initial step to screen MG patients in the perioperative period. Including Troponin T for hospitalized patients undergoing surgery may be beneficial to detect cardiac injury.

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## FOOTNOTES

**Author contributions:** Elmati PR designed the overall concept and outline of the manuscript; Elmati PR and Kogilathota Jagirdhar GS performed the research and literature review; Elmati PR, Kogilathota Jagirdhar GS, and Surani S analyzed the studies and wrote the

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