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Cardiac disorders worsen the final outcome in myasthenic crisis undergoing non-invasive mechanical ventilation: a retrospective 20-year study from a single center

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The study was performed to evaluate the impact of cardiological disorders on the outcome of myasthenic crisis (MC) requiring ventilation. The study includes 90 cases admitted to the Neurology Unit of Modena, Italy (January 2000 - September 2020). All patients were eligible for a non-invasive ventilation (NIV) trial. We analyzed the effect of cardiac comorbidities on the outcomes, which were the need of invasive ventilation, the risk tracheostomy for weaning failure and the duration of intensive care unit (ICU) stay Females were 58.9% and males 41.1%. Median age at diagnosis was 59 and at MC was 65. Patients were classified as early (EOMG) or late (LOMG), 34.4 and 65.6% respectively, according to age above or below 50; 85% of patients were anti- AChR antibody positive. Hypertension and cardiac diseases occurred at the diagnosis in 61 and 44.4%, respectively. Invasive mechanical ventilation (MV) was needed in 34% of cases. Nine subjects (10%) underwent tracheostomy because of weaning failure. Independent predictors of NIV failure were atrial fibrillation (AF), either parossistic or persistent (OR 3.05, $p < 0.01$), hypertensive cardiopathy (HHD) (OR 2.52, $p < 0.01$) and ischaemic heart disease (IHD) (OR 3.08, $p < 0.01$). Hypertension (HT) had no statistical effect on the outcomes. HHD was a predictor of weaning failure (OR 4.01, $p = 0.017$). Our study shows that HHD, AF and IHD increase the risk of NIV failure in MC receiving ventilation.

Key words: myasthenic crisis, atrial fibrillation, hypertensive heart disease, ischaemic cardiopathy, mechanical ventilation

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Introduction

Myasthenia gravis (MG) in an autoimmune disorder characterized clinically by fluctuating weakness of skeletal muscles [1-5]. Myasthenic crisis (MC) is a complication of MG characterized by worsening of weakness, resulting in respiratory failure that may require intubation and

mechanical ventilation1 [1-5]. We previously reviewed the predictors of outcome in a large population of MC, treated with non-invasive ventilatory support (NIV) outside the intensive care unit (ICU) setting [1]. Our study showed that the clinical parameters significantly associated with NIV failure and need of tracheal intubation were male gender, infections of upper respiratory tract, older age at onset and concurrent morbidities [1]. Hypertension and cardiac diseases were widely described in our cohort of myasthenic patients [1,4]. While we assessed the overall risk factors affecting prognosis, we faced the cardiac comorbidity burden. The aim of this study was to evaluate over a 20 year follow-up whether cardiological disorders could affect the prognosis of MC.

Material and methods

Study design and patient selection

We examined demographics data from 90 MG patients with MC published elsewhere [1]. All the subjects falling into the definition of Class V of MGFA [3], requiring ventilator support in our Neurology ward between January 2000 and September 2020 were enrolled. We excluded patients aged below 15 years and cases who were ventilated prior to the study entry or within 4 weeks after thymectomy. The ventilatory support was categorized as NIV and invasive. NIV was used to deliver bilevel positive airway pressure preferably with orofacial mask. In patients who failed NIV and underwent endotracheal intubation and mechanical ventilation (MV), the time duration of MV in days was determined and dichotomized for statistical purposes: less or more than 7 days to distinguish patients who have been early and successfully extubated from those who required prolonged MV. The follow up lasted from the first to the last visit or to death. Among our 90 cases, 29 (32.2%) exhibited more than 1 episode of MC for total number of 131 crisis. The study design was approved by the local Ethical Committee (N914/2020).

Examination at baseline and cardiological assessment

For age at onset, gender, antibody status and treatments we refer to previously reported data [1]. The cardiological assessments included clinical evaluation, basal and serial blood pressure, 12 -lead ECG and transthoracic echocardiography, when indicated. Cardiological disorders were categorized in ischemic heart (IHD), hypertensive heart (HHD), valvular diseases, rhythm and conduction abnormalities, requiring implantation of a pacemaker or of implantable cardioverter defibrillator. To prevent statistical bias, the type of incidental cardiac disease was defined for each patient enrolled at the time of diagnosis of MG and not during follow-up. Hypertension (HT) was defined following published guidelines [6,7]; we consider hypertensive all patients with resting and sustained blood pressure level above 140/90 mm Hg and/or those who were using antihypertensive medications [6,7]. In respect of HHD, the most widely accepted model of includes chronic pressure overload, development of left ventricular hypertrophy (LVH), due to progressive fibrotic changes, ultimately causing diastolic dysfunction, elevated LV filling pressures and diastolic heart failure [6,7]. LVH by ECG in our study was categorized using Sokolow-Lyon or Cornell criteria [8]. By echocardiography, an abnormal left ventricular mass (LVM) index was defined as greater than 110 gr/m^2 in women and 125 gr/m^2 in men [9]. The assessment of IHD was obtained from the patient's medical history and ECG, having in mind that the spectrum of myocardial ischemia ranges from no symptoms to myocardial infarction [10]. Cardiac conduction abnormalities included the atrial-ventricular (A-V) blocks II and III and cases, who needed implantable electric devices. We searched for history of atrial fibrillation (AF), either parossistic or permanent [11]. Valvulopathies aortic, mitral-tricuspidal, either congenital or acquired were classified according to current guidelines [12].

Outcome definition

Primary outcome of the study was NIV failure, defined as the need of tracheal intubation and invasive MV [1,3,5]. The decision to intubate the patient and start MV was made by the attending physicians on the basis of clinical and physiological criteria. In our Institution, the criteria used for elective intubation and MV in patients suffering from neuromuscular diseases are standardized as follows: vital capacity (VC) < 20 ml/kg or negative inspiratory force (NIF) < - 20 cmH2O, persistence of unsustainable work of breathing, refractory hypoxemia, persistent hypercapnia or acidemia despite NIV trial [1]. Other factors considered for elective tracheal intubation are bulbar dysfunction with inadequate airway protection, ineffective cough, retention of bronchial secretions and altered consciousness [1]. Secondary outcomes were the length of ICU stay, defined as the need for MV for a period of time longer or shorter than 7 days and the need of tracheostomy due to weaning failure. In patients who underwent MV, a weaning trial was considered when physiological parameters showed a clear evidence of improved respiratory muscles strength: maximum inspiratory pressure (MIP) > -20 cm H_2O, maximum expiratory pressure (MEP) > 40 cmH20, forced vital capacity (FVC) > 10 ml/kg [1]. Extubation was attempted when patients showed no clinical signs of respiratory fatigue during a spontaneous breathing trial with pressure support ventilation (PSV), in conjunction with physiologic parameter improvement (FVC of at least 15 ml/kg, MIP > - 20 cmH_2O, arterial

blood gases showing normal gas exchange). In patients who failed several weaning trials and/or showed no improvement of physiological respiratory muscle parameter after 15 days of MV, tracheostomy was performed with percutaneous dilatational technique.

Statistical analysis

Statistical analysis was performed using Stata 14.2 (Stata Corporation, College Station, TX, USA).Patient characteristics were analysed using descriptive statistics. Data were presented as median with minimum-maximum range or as mean with standard deviation (SD). For comparison between groups, Mann-Whitney U test was used for continuous variables and Mantel-Haenszel Chi Square Exact test for categorical variables. The impact of clinical variables was evaluated using logistic regression model. Crude and adjusted odd ratios (OR) were obtained after adjustment with risk factors for NIV. Interactions between variables were tested as well. Violin plot was used in explanatory data analysis visually showing the numerical distribution of data and skewness through displaying the percentiles and averages. Margins statistic computed marginal predictions based on a previously fitted regression model. We calculated the area under the receiver operating characteristic curve (AUC) which ranges from 0.5 to 1 (perfect discrimination). Receiver Operator Characteristic (ROC) curves were obtained from plotting true positive rate versus false positive rate. Multiple imputation chained equation method (MICE) was used to impute and estimate missing data regarding cardiological predictors using [13].

Results

Baseline clinical characteristics of the patients

Table I summarizes the demographic data at baseline. Median age of onset was 59 (Range 15-88, IQR 33). Median age of MC was 65 (IQR 31). Duration of follow up ranged from 13 (2 cases) to 577 months (IQR 150). HT vas detected in 61.1% and selected cardiological disorders in 44.4%, whereas missing data in 11% of cases were imputed and estimated statistically with the MICE method [13]. Table II summarizes the cardiological diagnoses with the prevalence of each phenotype at the time of diagnosis of MG. The cardiological disorders prevailed significantly in LOMG (p = 0.001), whose mean age was 67 years. The patients with AF were 17% of overall MC; among those, 86.6% had LOMG and only 2 (13.3%) were females. Patients with LOMG represented 84.6% of IHD and only 3 (27%) were females. HHD represented 62 % of overall proven cardiac disorders at diagnosis and 88% had LOMG.

By the end of follow-up, HHD and AF were coincidentally observed in 37.5% of patients; indeed HHD and AF share common pathogenetic risk factors [10,11]. In respect of the antibody status, 93% of patients with AF had antibodies to AChR and subjects with HHC and IHD were respectively 84% and 77% antibody positive. Among the 25 patients with thymomas, 4 cases had AF (16%) whereas 12 and 28% had IHD or HHC, respectively. Valvulopathies involving mitral-tricuspidal and aortic valves were never severe and always incidentally found by echocardiography.

Table I. Demographic characteristics at baseline (n = 90).

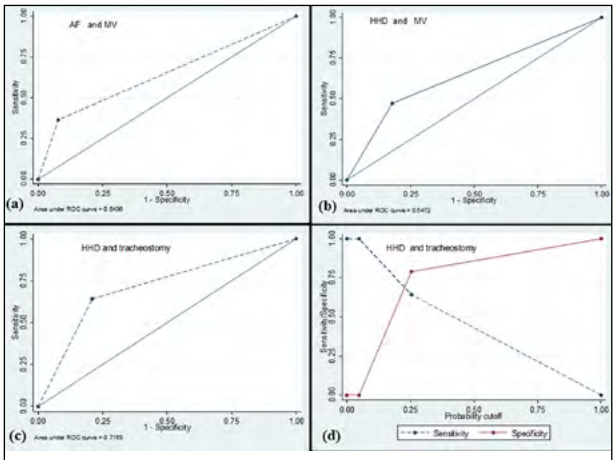
Variables		**n %**
Gender	Male	37 (41.1%)
	Female	53 (58.9%)
Age at onset (years) [median (range)]		59 (16-88, IQR 33)
	Early onset (EOMG)	31 (34.4%)
	Late onset (LOMG)	59 (65.6%)
Antibody profile [n (%)]	Anti-AChR Abs	77 (85.6%)
	Anti-MuSK Abs	3 (3.3%)
	Double seronegative	10 (11.1%)
Cardiovascular comorbidities at diagnosis	Hypertension	55 (61.1%)
	Cardiological diseases	40 (44.4%)
Other comorbidities at diagnosis	Autoimmune diseases Metabolic, endocrine diseases	34 (37.8%) 21(23.3%)
Multiple comorbidities ≥ 3 at diagnosis		39 (43.3%)
Thymectomy Thymoma Thymic hyperplasia		45 (50%) 25 (27.6%) 15 (16.7%)

Abbreviations. Abs: Antibody; AChR: AcetylCholine Receptor; EOMG: Early onset onset myasthenia gravis; LOMG: Late onset myasthenia gravis; MuSK: Muscle Specific tyrosine Kinase; MGFA: Myasthenia Gravis Foundation of America; MC: Myasthenic crisis; IS: Immunesuppressant; IQR: Interquartile range

Table II. Cardiac morbidities detected at MG diagnosis in our 90 patients.

Type of cardiopathy	Incidence [n (/%)]
Conduction defects	14 (15%)
Arrhythmias (AF)	15 (17%)
Ischemic heart disease (IHD)	13 (14%)
Hypertensive heart disease (HHD)	25 (28%)
Valvular diseases (mitral – tricuspid or aortic)	14 (15%)
Not defined cardiological phenotypes	10 (11%)
Hypertension (HT) without HHD	55 (61.1%)
Overall cardiac disorders	40 (44.4%)

Abbreviations. AF: Atrial Fibrillation; IHD: Ischaemic Heart Disease; HHD: Hypertensive Heart Disease; HT: Hypertension: MG: myasthenia gravis. The number in brackets illustrate the prevalence of each types of cardiac disorders at the time of MG diagnosis.



Abbreviation. AF: Atrial Fibrillation; AUC: Area under the curve; HHD: Hypertensive Heart Disease; MV: Mechanical ventilation; ROC: Receiver Operator Characteristic

Figure 1. A-B) ROC curves indicating a good discrimination for MV of AF and HHD (AUC = 0.64); C) ROC curve shows a good discrimination of HHD for the risk of tracheostomy (AUC = 0.71); D) ROC curves indicates sensitivity and specificity for the best cut -off of HHD as predictor for tracheostomy.

Primary and secondary outcomes

NIV failure followed by tracheal intubation were documented in 34 patients (37.7%). Table III depicts the crude and adjusted odd ratios (OR) for the risk of MV in each cardiological phenotype. Independent predictors of ventilation were AF (OR = 3.05; p < 0.01), HHD (OR = 2.52 p = < 0.01) and IHD (OR = 3.08; p = 0.01), whereas the presence of HT had no statistical effect on this outcome (p = 0.52). Interestingly, we found that the presence of conduction abnormalities almost doubled the risk of MV (OR = 2.14, p = 0.025), but this variable was not an independent predictor after adjustment with sex and age. Our female patients exhibited a lower risk of ventilation than males already at the base line (p = 0.003). By testing the interactions between variables (i.e AF, HHD and IHD), sex or age at onset, no results were statistically significant. Figures 1A and B depict the ROC curves, which showed good discrimination of AF and HHD as predictors of MV (AUC = 0.64). Figure 1C shows good sensitivity of HHD for risk of tracheostomy (AUC = 0.71) and figure D) depicts the sensitivity and specificity for the best cut-off of HHD as predictor for tracheostomy. Among the 34 patients who showed NIV failure and need of invasive MV, 64.7% had ICU stay longer than 7 days. Table IV shows the crude and adjusted ORs for the risk of ICU duration more than 7 days; neither AF nor IHD nor HHD had a statistical significant effect. Interestingly, patients who experienced more than 2 episodes of MC needed longer ICU stay (OR = 12, p < 0.01). Figures 2A and B illustrate the impact of recurrent MC on the risk of longer duration of ICU stay (AUC = 0.72). Tracheostomy due to failure of extubation was needed in 10% of the whole cohort and in 26.4% of the patients, who had undergone previously to invasive MV. HHD was an independent predictor of extubation failure (OR = 4.01, p = 0.017), as shown in Table V. Figure 2C illustrates the interaction between probability of tracheostomy, male gender and HHD. The probability increases in males with HHD. The violin plots

Table III. Crude and adjusted odd ratios for the risk of mechanical ventilation (MICE * see methods for details).

Variables	Crude OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Atrial fibrillation (AF)	5.08	3.01-8.56	**< 0.01**	3.05	1.6-5.53	**< 0.01**
Hypertensive heart disease (HHD)	4.1	2.30-7.4	**< 0.01**	2.52	1.32-4.81	**< 0.01**
Ischaemic heart disease (IHD)	5.7	2.69-12.3	**< 0.01**	3.08	2.69-12.3	**< 0.01**
Hypertension (HT)	1.5	0.64-3.8	0.32	1.45	0.46-4.6	0.52
Altered conduction	2.1	1.1-4.1	**0.025**	1.13	0.52-2.48	0.74
Valvulopathies	1.20	0.50-2.86	**0.68**	1.22	0.47-3.16	0.67

Abbreviations. AF: Atrial Fibrillation; IHD: Ischaemic Heart Disease; HHD: Hypertensive Heart Disease; MICE*: multiple imputation chained equation. OR: odd ratio. Significant results in bold.

Table IV. Crude and adjusted odd ratios for the risk of more than 7 days in ICU (MICE* see methods for details).

Variables	Crude OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Atrial fibrillation (AF)	1.5	0.87-2.64	0.13	0.65	0.15-2.79	0.56
Hypertensive heart disease (HHD)	2.83	0.86.-9.30	0.086	3.4	0.89-13.2	0.072
Ischaemic heart disease (IHD)	1.16	0.29-4.6	0.82	1.12	0.29-4.32	0.86
Hypertension (HT)	1.5	0.32-7.1	0.59	1.72	0.29-10.2	0.54

Abbreviations. AF: Atrial Fibrillation; IHD: Ischaemic Heart Disease; ICU: Intensive Care Unit; HHD: Hypertensive Heart Disease; MICE*: multiple imputation chained equation. OR: odd ratio

Table V. Crude and adjusted odd ratios for the risk of tracheostomy. (MICE * see methods for details).

Variables	Crude OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Atrial fibrillation (AF)	1.15	0.30-4.2	0.83	0.29	0.07-1.81	0.084
Hypertensive heart disease (HHD)	6.7	2.37-19.2	< 0.01	4.01	1.27-12.5	0.017
Ischaemic heart disease (IHD)	1.27	0.34-4.7	0.72	1.4	0.51-3.8	0.51
Hypertension (HT)	2.4	0.47-123.3	0.29	2.5	0.35-18.4	0.34

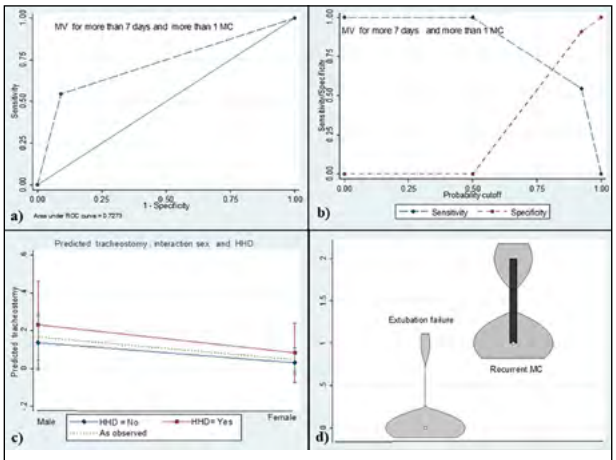
Abbreviations. AF: Atrial Fibrillation; IHD: Ischaemic Heart Disease; HHD: Hypertensive Heart Disease; MICE*: multiple imputation chained equation. OR: odd ratio

in Figure 2D (supplementary material) illustrate the overall occurrence of extubation failure and MC recurrence. The white circles represent the median.

Discussion

We previously demonstrated that in patients with MC, NIV failure may occur only in a third of cases [1]: NIV failure was significantly associated with male gender, respiratory tract infections, older age at onset, concurrent morbidities [1]. Here, we retrospectively analyzed whether cardiac comorbidities in MCs demanding ventilation could affect the need of MV, the length of ICU care and the risk of extubation failure. Notably, mostly of our patients had old age; indeed this finding is unavoidable, fully reflecting the prevalence of LOMG in recent years, in the world [4,14-17]. Age and morbidity rate are considered risk factors for longer intubation and poor outcome by several authors [14,17,21-24]. Misra et al. [17] found a significant incidence of coronary artery diseases and hypertension among their LOMG patients, whereas Sivadasan et al. [14] described cardiac disorders only in 12 patients (19%) out of 62 followed in Neuro-ICU; possibly, such low incidence is due to the fact that these authors [14] did not analyse in details the types of cardiopathies.

Extubation failure in MC reached in some studies the incidence of 35%, increasing with older age and pneumonia [20,22]. Murthy in his editorial [21] observed that cardiac complications are predictors of mortality in MC; moreover in the work of Thomas et al. [22], the precipitating factors causing death were sepsis and respiratory failure, due to several conditions, including congestive heart failure. Older age and respiratory failure were predictors of death in a large US cohort of 5,502 patients, whereas the cardiac complications, although highly observed, did not independently predict mortality [23]. Liu et al. [24] found that the non-MG related factors, including preceding strokes,



Abbreviations. AUC: Area under the curve; MV: Mechanical ventilation; MC: Myasthenic crisis; HHD: Hypertensive Heart Disease; ICU: HHD. Intensive care unit

Figure 2. A) Receiver Operator Characteristic (ROC) curves indicating the sensitivity of more than 1 episode of MC for predicting more than 7 day duration of ICU stay (AUC = 0.72); B) The ROC curve for best cut-off that maximizes sensitivity and specificity of recurrent MC for this outcome; C) Predicted risk of trachestomy: interaction between gender and presence or absence of HHD. The graph shows that the probability of tracheostomy increases with male gender and presence of HHD. Dashed line. as observed in the model. Line with diamond symbol = without HHD. Line with square = with HHD; D) The violin plots illustrate the overall occurrence of extubation failure and MC recurrency. The circles are the median.

AF, hyperlipidemia, myocardial infarction were closely linked with death. In our study AF, HHD and IHD independently predicted NIV failure, whereas only HHD had impact on extubation failure.

The effect of cardiological morbidities on MV need in MC requires attention [21,22]. The heart and lung are anatomically coupled as they occupy the same thoracic cavity, connected via blood vessels. Pressure changes within the thoracic cavity during the respiratory cycle affect the pressure systems to the heart and from the heart to the extra-thoracic spaces [25,26]. Johannessen et al. [27] showed that LV diastolic filling differed significantly in patients with MG compared to age and heart-rate matched controls; however in their patients, the systolic function was normal at the baseline. These authors [27] concluded that age, filling pressure and myocardial ischemia influenced the LV compliance. Later on, Owe et al. [28] reported that the frequency of heart disease or increased mortality due to heart disease between 1951 and 2011 in MG patients was equal in Norway to the prevalence among the general population. According to Gilhus et al. [29], MG patients do not seem to have more frequent manifest heart disease or increased heart disease mortality; however, attention should be given to patients with thymoma associated MG and to LOMG, exhibiting antibodies to titin, striated muscles, anti-Kv 1.4, ryanodine receptors, where the heart muscle can be target of an autoimmune inflammation [29,30].

Why, in our study, some cardiologic morbidities showed significant impact on weaning failure is still under discussion. Patients suffering from MC show a reduction in strength of respiratory muscles and might be more prone than normal subjects to develop diaphragm fatigue and respiratory pump failure [31,32]. In addition, current evidences demonstrate that inspiratory dysfunction may occurs with aging and is accentuated by overlapping chronic heart failure [31,32]. In particular, physiological studies showed that age is inversely correlated with maximal inspiratory pressure (MIP), with faster decline for subjects older than 65 years. The pathophysiological process behind this age-related inspiratory dysfunction probably reflects muscular abnormalities due to sarcopenia [33].

Moreover, different studies suggest that inspiratory muscle dysfunction due to age may be exacerbated by an overlapping, even subclinical chronic heart failure [32-34]. Indeed, respiratory muscle test obtained from volitional as well as non-volitional procedure (through phrenic nerve stimulation), showed clearly a decreased of maximal inspiratory pressure generated by diaphragm in patients affected by chronic heart failure, which is age dependent [34]. Furthermore, patients affected by chronic heart failure showed reduced ability to perform inspiratory efforts against a sub-maximal pressure threshold load [35]. Despite the molecular mechanisms underlying diaphragm abnormalities in humans with chronic heart failure remain poorly understood, a recent study analysing diaphragm biopsies revealed a severe diaphragm myopathy that occurs independently from disuse, aging or obesity [36]. Furthermore, the same study showed that diaphragm weakness was associated with intracellular abnormalities, as fiber atrophy, oxidative stress, mytochondrial dysfunction, impaired Ca2+ homeostasis and elevated proteasome-dependent proteolysis [36]. Indeed, the molecular and physiological changes of diaphragm, associated with aging and cardiovascular disorders, could promote the diaphragm task failure during the MC.

Our study analyses a predominantly elderly population; the prevalence of AF and cardiovascular disorders in the Western world general population during the past 20 years showed increased rate for both men and women [10,11]. According to ESC guideline [6,10,11], the heart failure is defined as a clinical syndrome due to a structural and/or functional abnormality of the heart, resulting in elevated intracardiac pressure and/or inadequate cardiac output at rest and/or during exercise. Historically, studies investigating HHD have primarily focused on LV hypertrophy, but it is increasingly apparent that HHD encompasses a range of target-organ damage beyond LV, including other cardiovascular structural and functional adaptations that may occur separately or concomitantly [7,37]. Chronic heart failure is the result of cardiological disorders of different aetiology; in our study the definition HHD could hide patients with diastolic dysfunction, falling within the phenotype of chronic heart failure with preserved ejection fraction, as previously state in the original work by Johannssen et al. [27].

Recent studies highlighted the fact that cardiac dysfunction is cause of weaning failure. Indeed weaning shares some similarities with a cardiac stress test [32,35]. Moreover, the shift from MV to spontaneous breathing might induce several events. Firstly, a negative intrathoracic pressure increases the systemic venous return pressure gradient, the RV preload, the central blood volume and the LV preload; secondly it increases the surrounding pressure of the LV with increase in LV afterload [32,35] and finally, an increase in the work of breathing is accompanied by an enhanced adrenergic tone, as documented by serum catecholamine levels [37-40]. Overall these mechanisms could provoke an increase in pulmonary arterial occlusion pressure and an increase in LV filling pressure. In addition in case of MV need, inspiration-associated over-inflation of lung volume will enhance the pulmonary vascular resistance with increased RV afterload, ultimately leading to pulmonary edema [39,40]. Given that, we can conclude that cardiological disorders in patients with MCs may increase the risk of NIV failure via several dynamic mechanisms.

Intravenous immunoglobulins (IVIg) was the first-line therapy administered in 71% of our MC during the last decade, whereas the cases with faster neurological deterioration and/or required longer ICU stay were more frequently treated with plasma exchanges (PE) [1]. Treatment with IVIg in our hands was preferred to PE in older patients, especially if affected by sepsis [2,29]. During MC, we avoided steroids because patients with poor control of MG and eventually associated pneumonia are at risk of worsening [1,17,18,21,22].

As stated by Murthy [21], there is no specific therapy for cardiac involvement in MG and in MC. Over the years, the cardiologists in our Institution tended to maintain the baseline therapies given for AF, IHD and HHD. Indeed, the natural history of MG could be modified by drugs given because of associated pathologies, but this issue in patients remains uncertain, because the data are limited with a lack of systematic studies [14]; for instance, we are not sure whether the usage of aspirin and statins in MG patients with associated cardio-cerebrovascular diseases could change their long-term outcome. At this point, we have to remember that MG patients often undergo lifelong therapy with anticholinesterase agents (AChEI) and we should have clear the potential adverse action of AChEI in worsening cardiological symptoms, including coronary vasospam and A-V blocks [42,43]. Prado et al. [44] stated that cardiac dysrhythmia attributed to hypercholinergic crisis is one of the fatal complications observed in MC. In addition, the concerns about sudden cardiac death secondary to cardiac autonomic neuropathy in the elderly, warrant a close follow-up with attention to drugs as cardioselective beta-blockers and amiodarone [14].

Conclusions

Our single center study was retrospective, based on serial assessments by the same physicians over 20 years. There are limitations in the study: first, the results might not be extended to MG in general. Second, it was impossible to acquire accurate weaning details, because decisions came certainly from judgment of clinicians having in charge the patients. Third, the evolution of cardiac parameters after MC was not obtained as the patients were followed with an ambulatory care. The impact of cardiac comorbidities on MC should be known by clinicians, because the interactions between respiratory muscles and heart are challenging for patients and doctors.

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None.

Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

EI,MM, AA provided data and revised drafts. EB,VA,MG evaluated the patients details. GG wrote and revised the draft and made statistical analysis. AM revised the final drafts.

Ethical consideration

This study was approved by the Institutional Ethics Committee AVEN (914/2020).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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