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Increased heart rhythm in response to high-dose intravenous methylprednisolone pulse therapy of moderate-to-severe Graves' orbitopathy

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ABSTRACT

Background. Intravenous glucocorticoids pulses administration is the main therapeutic option in the treatment of Graves' orbitopathy. Such therapy could relate to the multiple adverse effects. The aim of the study is evaluation the influence of intravenous methylprednisolone (IVMP) pulse therapy on the heart rhythm (HR) changes in patients with active, moderate-to-severe Graves' Orbitopathy (GO).

Methods. We studied 20 patients with moderate-to-severe GO. All patients received 12 IVMP pulses (6 x 500 mg plus 6 x 250 mg) at equal time intervals in a weekly schedule. We performed Holter ECG monitoring for 3 consecutive days (the day before, the day of IVMP and day after IVMP) to monitor HR and arrhythmias. We compared changes in HR between these 3 days and set time interval when the alteration was significant. This evaluation was performed during the 1st, 6th and 12th IVMP pulse.

Results. Increased HR, in comparison with the day before, was registered on the day of IVMP administration. The most significant increase in HR started 5 hours (h) after a pulse administration and lasted 12 h. There were no significant differences in HR between the day before and the day after IVMP. We did not notice any major adverse cardiac events including severe arrhythmias.

Conclusions. IVMP therapy is associated with increased HR, that occurs a few hours after infusion, lasts several hours and is transient.

Introduction

High doses of intravenous glucocorticoids (GCs) are commonly used as a treatment for many autoimmune and inflammatory disorders. According to the European Group on Graves' Orbitopathy (EUGOGO) guidelines, intravenous methylprednisolone (IVMP) is an accepted first-line agent for active, moderate-to-severe and very severe Graves' orbitopathy (GO) [1]. This treatment is proven to be more efficient and safer than oral GCs. For active, moderate-to-severe GO it is recommended to treat patients with twenty IVMP pulses once weekly for 12 weeks. In the first 6 pulses, the dose is 0.5 g IVMP and for the next 6 weeks, it is reduced to 0.25 g IVMP.

However, some patients may experience adverse cardiovascular effects during the administration of iv. GCs, which in rare cases may even be fatal. There are limited data, mostly obtained from case reports, reporting the occurrence of venous thromboembolism, cardiac arrhythmias, acute myocardial infarction or acute heart failure [2]. Increased heart rhythm (HR) has drawn our attention as a possible adverse effect correlated with IVMP [3, 4]. During this study, we performed 72-hours of Holter monitoring to evaluate the impact of IVMP on patients with moderate-to-severe GO, concerning HR changes and arrhythmias.

Material and Methods

Study population

This observational study was conducted at the Department of Internal Medicine and Endocrinology at the Medical University of Warsaw between 2011 and 2015. 20 consecutive patients (14 women and 6 men) with active, moderate-to-severe GO treated with IVMP pulse therapy following EUGOGO, were enrolled in the study. The inclusion criteria were: (1) age ≥ 18 years; (2) euthyroidism (patients with hyperthyroidism treated with antithyroid drugs, after radiotherapy/surgical treatment on levothyroxine (L-T4) therapy, if necessary, with euthyroid Graves' disease, or with Hashimoto's disease on L-T4 therapy; and (3) completion of 12 IVMP pulses. Patients with previous GCs treatment in the last 6 months were excluded from the research. Clinical characteristics of patients are shown in **Table 1**.

Ethical statements

This research was approved by the bioethics committee at the Medical University of Warsaw, Poland. Each patient submitted written consent before the study.

Table 1. Clinical characteristics of the patient population.

Male, n (%)	6 (30)
Female, n (%)	14 (70)
Age, years (mean ±SD)	51 ± 11
Etiology of GO	
Graves' disease, n (%)	15 (75)
Hashimoto's disease, n (%)	5 (25)
Smoking	
Current smokers, n (%)	10 (50)
Past smokers, n (%)	7 (35)
Non-smokers, n (%)	3 (15)
Comorbidities	
Hypertension, n (%)	9 (45)
Medications	
Beta-blockers, n (%)	7 (35)
ACEI, n (%)	6 (30)
ARB, n (%)	1 (5)
Calcium-blockers, n (%)	5 (25)
Statins, n (%)	5 (25)
Diuretics, n (%)	1 (5)
L-thyroxine, n (%)	14 (70)
Antithyroid drugs, n (%)	7 (35)
Laboratory measurements	
TSH, (range: 0.27–4.2 µIU/mL)	2.2 ± 1.5
fT4, (range: 12–22 pmol/L)	16.6 ± 3.7
TBII, (N < 1.73 IU/L)	5.9 ± 4.7

GO – Graves' Orbitopathy; AITD – Autoimmune Thyroid Disorder; ACEI – Angiotensin Converting Enzyme Inhibitors; ARB – Angiotensin Receptor Blockers; TSH – thyreotropin; fT4 – free thyroxine; TBII – thyreotropin binding inhibitor immunoglobulin; Laboratory tests (TSH, fT4, TBII) are shown as a mean value ± standard deviation (SD).

Study design and 24-hour Holter ECG monitoring

All participants received IVMP pulses following EUGOGO recommendations (cumulative dose of methylprednisolone 4.5 g, treatment duration 12 weeks in once-weekly iv. pulses, each pulse in the first 6 weeks 0.5 g MP and next 6 weeks 0.25 g MP). Each pulse was administered at the same time interval (10–12 a.m.). The clinical status of patients was evaluated before each pulse, including blood pressure monitoring, glucose level monitoring and symptoms of infection.

A 24-hour Holter ECG monitoring was carried out with EXCEL 2 by Medilog Oxford and ROZINN by Margot Medical. HR was measured hourly for 3 consecutive days (the day before, the day of IVMP and the day after IVMP) during 1st, 6th and 12th

IVMP pulse. For every pulse, we performed 3 analyses comparing mean, minimal and maximal circadian HR between (1) the day before and the day of IVMP, (2) the day of IVMP and the day after IVMP, (3) the day before and the day after IVMP. To define the exact time of the most significant difference between HR we compared mean, minimal and maximal HR from corresponding hours between the day before and the day of IVMP. We set the time interval of the first and the last hour of the day when a significant difference in HR between compared days was observed. For this period, the average HR for each patient was calculated. We performed a statistical analysis comparing average HR between the day before IVMP and the day of IVMP, for the defined time interval. Lastly, we searched for severe arrhythmias in 24-hour Holter ECG monitoring.

Statistical Analysis

Statistical analysis was performed using version 13.3 Statistica software. Continuous variables were demonstrated as mean ± standard deviation (SD) or median values (lower quartile-upper quartile). Categorical data were presented as numbers (n) or percentages (%). Comparisons between mean, maximal and minimal circadian HR were assessed before and after selected IVMP pulses using a non-parametric Wilcoxon signed-rank test. Results including p-value <0.05 were considered statistically significant.

Results

Increase in mean, minimal and maximal circadian HR on the day of IVMP administration compared to the day before was found in all analyzed pulses ($p < 0.001$ for 1st, $p < 0.001$ for 6th, $p < 0.005$ for 12th) (see **Table 2**). There were no statistically significant differences observed in mean, minimal and maximal circadian HR, including all pulses between the day before and the day after IVMP infusion. Mean HR from corresponding hours was compared between the day before and the day of IVMP. Significant increase in HR, concomitantly in all pulses, was noticed for the first time at 5 p.m. This significant change in HR, between the day before and the day of IVMP was recurrent at every hour until 5 a.m. On this basis, precise timeline representing a significant change in heart rate starts on the day of IVMP at 5 p.m. and lasts for 12-h, until 5 a.m. the following day. During this period, a significant increase in mean, minimal and maximal HR was found between the day before and the day of IVMP administration (see **Table 3**). This increase in median HR was 18% for 1st and 6th pulse and 17% for 12th pulse. In the group with beta-blockers (35% of patients) we observed the same trend of changes in HR. None of our patients developed major adverse cardiovascular events or serious heart rhythm disturbances. However, we observed some mild and transient arrhyth-

Table 2. Changes in mean, maximal and minimal circadian heart rhythm on the day before, the day with and the day after intravenous methylprednisolone (IVMP) administration during 1st, 6th, 12th pulse.

IVMP Pulse (circadian)	Day Before Pulse Median (Q1–Q3, n/min)	Day With Pulse Median (Q1–Q3, n/min)	Day After Pulse Median (Q1–Q3, n/min)
Mean HR			
1st	77 (69–80)	82 (80–88)	78 (70–86)
6th	76 (68–77)	86 (80–88)	81 (74–87)
12th	80 (73–83)	85 (79–88)	76 (70–83)
Maximal HR			
1st	90 (82–94)	96 (92–102)	93 (82–100)
6th	89 (82–91)	99 (93–103)	94 (84–99)
12th	93 (83–96)	98 (91–102)	89 (82–97)
Minimal HR			
1st	62 (57–66)	69 (67–72)	65 (56–72)
6th	62 (56–64)	70 (67–75)	69 (61–74)
12th	67 (61–70)	70 (67–74)	65 (58–70)

HR: average heart rhythm [n/min], Q1: lower quartile, Q3: upper quartile.

mias during ECG monitoring, such as: supraventricular extrasystoles, ventricular extrasystoles, supraventricular tachycardia, supraventricular and ventricular pairs. None of patients suffered from atrial fibrillation. Some of patients reported feeling of tachycardia after IVMP infusion which was without any additional side effect, and they described as a mild disorder.

Table 3. Changes in mean heart rhythm during 12-h time interval (5 p.m.–5 a.m.) on the day before and the day with intravenous methylprednisolone (IVMP) during 1st, 6th, 12th pulse. P-value was assessed using a non-parametric Wilcoxson signed-rank test.

IVMP Pulse (5 p.m.–5 a.m.)	Day Before Pulse Median (Q1–Q3, n/min)	Day With Pulse Median (Q1–Q3, n/min)	p-value
Mean HR			
1st	69 (66–76)	82 (79–88)	<0.001
6th	69 (66–75)	82 (79–90)	<0.001
12th	73 (68–80)	83 (78–88)	<0.002
Maximal HR			
1st	82 (77–90)	96 (91–101)	<0.001
6th	83 (76–88)	97 (93–103)	<0.001
12th	83 (77–92)	96 (90–102)	<0.005
Minimal HR			
1st	57 (56–63)	70 (67–75)	<0.001
6th	57 (56–62)	68 (67–76)	<0.001
12th	64 (60–68)	70 (65–75)	<0.002

HR: average heart rhythm [n/min], Q1: lower quartile, Q3: upper quartile

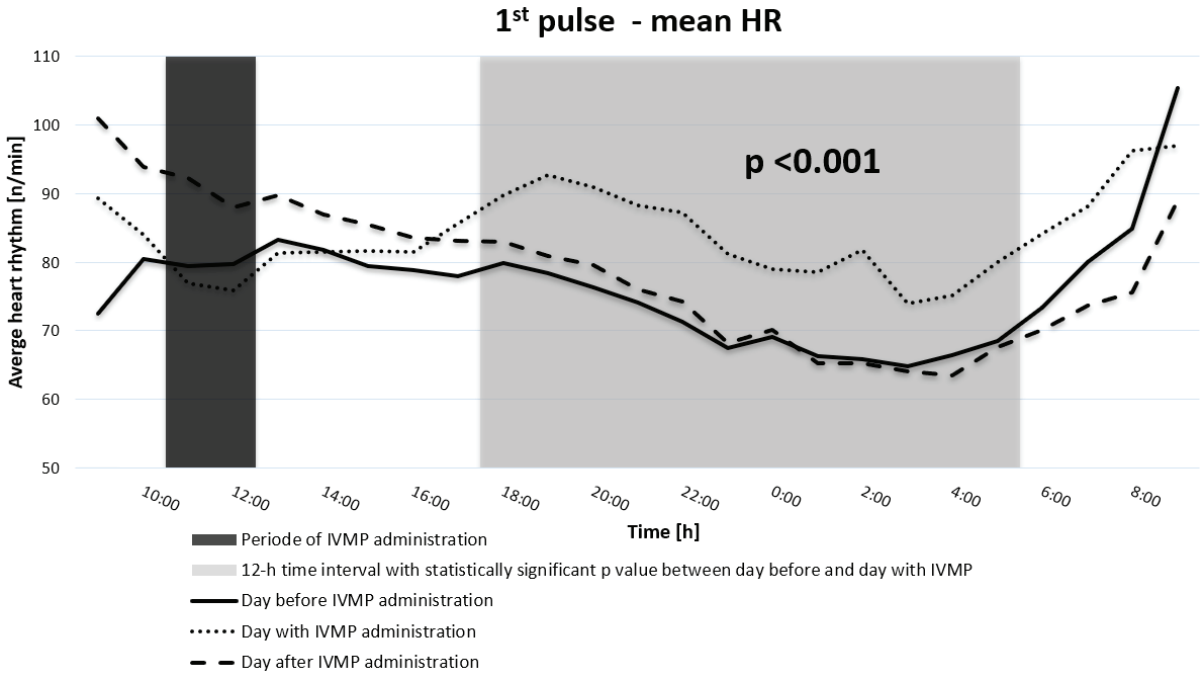

Figure 1. Average HR variabilities within the day before, the day of IVMP and the day after 1st IMVP administration. P-value shows mean HR comparison for a 12-h time interval (5 p.m.–5 a.m.) between the day before and the day of drug infusion. P-value was assessed using a non-parametric Wilcoxon signed-rank test.

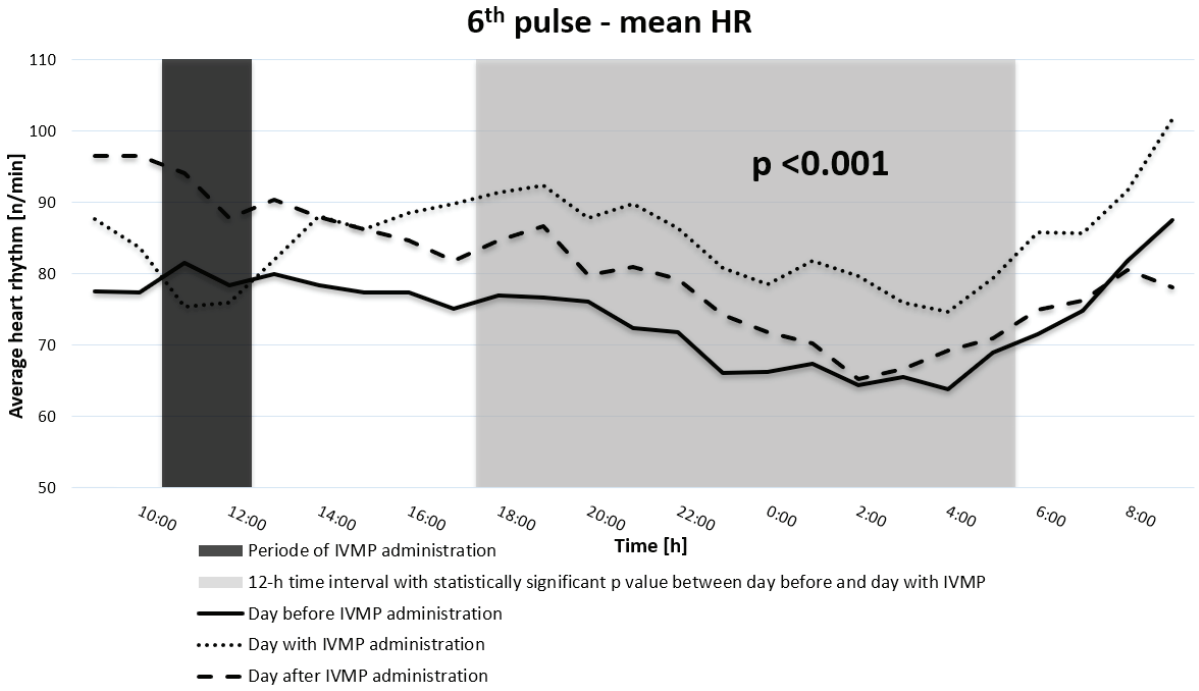

Figure 2. Average HR variabilities within the day before, the day of IVMP and the day after 6th IMVP administration. P-value shows mean HR comparison for a 12-h time interval (5 p.m. – 5 a.m.) between the day before and the day of drug infusion. P-value was assessed using a non-parametric Wilcoxson signed-rank test.

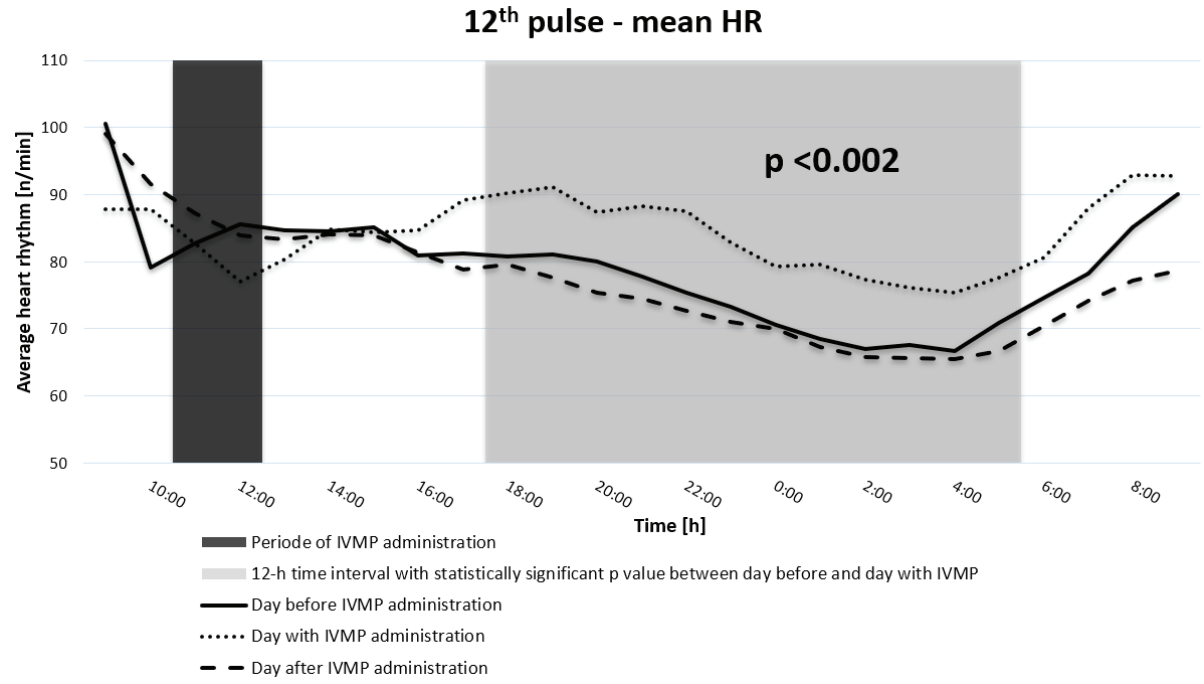

Figure 3. Average HR variabilities within the day before, the day of IVMP and the day after 12th IMVP administration. P-value shows mean HR comparison for a 12-h time interval (5 p.m. – 5 a.m.) between the day before and the day of drug infusion. P-value was assessed using a non-parametric Wilcoxon signed-rank test.

Discussion

GO is the main extrathyroidal manifestation of Graves' disease, though severe forms are rare [1]. IVMP is a well-established first-line treatment for moderate-to-severe active GO with better response rate and tolerance than oral GCs. However, there are reports of serious adverse effects associated with this therapy [2, 5], Cardiovascular disorders and various arrhythmias after corticosteroid pulse therapy have been observed in several diseases [2, 5–7].

Most commonly, cardiac arrhythmias described as related to IVMP were ventricular tachycardia [8], bradycardia [9] and atrial fibrillation [10–12]. However, there were also described cases of cardiovascular collapse [13], cardiocirculatory arrest [14] and sudden death [15]. A range of these serious cardiac arrhythmias can be observed shortly after methylprednisolone (MP) infusion [3] as well as during late hours after treatment [8, 9]. Although it seems that proarrhythmic impact of IVMP depends on the dose and the type of used drug, the mechanism remains unclear.

In Miśkiewicz et al. [16] study the impact of IVMP on blood pressure (BP) and N-terminal pro-brain natriuretic peptide level was investigated. Increase in maximal systolic BP and mean nocturnal BP was observed with a higher prevalence of non-dipping BP profile. The results suggested a cumulative effect of IVMP on BP with compensatory higher brain natriuretic peptide.

In the presented study, HR was significantly higher on the day of IVMP administration in comparison to the day before and the day after infusion. Besides, the change of HR was significantly greater 5-h after IVMP infusion, in the 12-h time interval (5 p.m.–5 a.m.) with an average increase of 20% for all pulses. Our results are consistent with previous reports by M. Pishgahi et al. [3] and Fujimoto et al. [4] in which significant increase in HR after pulse therapy was detected, including ventricular tachycardia in the second study. However, ECG monitoring could not accurately elucidate changes in cardiac rhythm. Both authors suggested that these dysrhythmias might be an effect of acute shift of potassium across the cell's membrane. Glucocorticoids, like methylprednisolone, can alter electrolyte levels, particularly potassium and sodium, through their activation of the mineralocorticoid receptor (MR). This leads to changes in sodium reabsorption and potassium excretion, which help regulate salt concentration in the body. While methylprednisolone has minimal mineralocorticoid activity, high doses of the drug may bind to the mineralocorticoid receptor in the collecting duct and increase these effects [17]. Low potassium levels (hypokalemia) can affect the resting membrane potential of heart cells and reduce repolarization reserve, increasing the risk of tachyarrhythmias such as Torsade's de pointes and polymorphic VT, which can progress to ventricular fibrillation and sudden cardiac death [18]. Although the blood levels of sodium and potassium were not measured in the study, an increase in heart rate observed in the study supports the hypothesis that the intravenous use of methylprednisolone may be contributing to these effects through its hypokalemic effects.

Bradyarrhythmias were not observed in our study. Our findings are inconsistent with results obtained by Tvede et al. [9], who noted a one-week decline in heart rhythm in all 5 patients after they received MP. Similar report by Yong et al. [19] presented significant decrease in mean HR during the 1.5-h time interval after IVMP administration with no cumulative effect. What is also important in our study, 35% of analyzed patients were exposed to beta-blockers. This group was not statistically different in the HR changes and incidence of cardiac arrythmias.

Our report indicates that IVMP therapy is associated with increased HR after each pulse. The change in HR is transient and last only on the day of IVMP infusion. None of our patients developed major cardiovascular adverse events or serious heart rhythm disturbances. Most of the patients reported feeling of tachycardia after IVMP infusion but was described as a mild side effect. However, elderly or obese patients with cardiovascular comorbidities may have a higher risk of developing cardiac adverse events [6]. We did not observe difference between group with and without betablockers, but our patients were without severe cardiac diseases. In the group of patients with higher risk of cardiac exacerbation, routine betablocker therapy should be considered with cardiac rhythm monitoring. The mechanism of influence of IVMP is not clear and needs further investigation.

Limitations

This study has some limitations. There was a small group of patients and our trial did not investigate the underlying cause of the increased heart rhythm after IVMP.

Conclusions

Therapy with IVMP is associated with increased HR which occurs a few hours after infusion. Changes in heart rate (about 20%) last several hours, are transient and do not lead to any adverse cardiovascular events. Future research needs to be performed to provide greater insight into the correlation between IVMP and HR.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

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There are no sources of funding to declare.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, Marinò M, Vaidya B, Wiersinga WM; EUGOGO †. The. 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021 Aug 27;185(4):G43-G67. doi: 10.1530/EJE-21-0479. PMID: 34297684.
2. Miśkiewicz P, Kryczka A, Ambroziak U, Rutkowska B, Główczyńska R, Opolski G, Kahaly G, Bednarczuk T. Is high dose intravenous methylprednisolone pulse therapy in patients with Graves' orbitopathy safe? Endokrynol Pol. 2014;65(5):402-13. doi: 10.5603/EP.2014.0056. PMID: 25301492.
3. Pishgahi M, Dadkhahfar S, Robati RM, Kheradmand Z, Shahidi-Dadras M, Zargari O, Elpern DJ. Electrocardiographic changes after high-dose corticosteroid pulse therapy in pemphigus patients. J Dermatolog Treat. 2018 Dec;29(8):802-805. doi: 10.1080/09546634.2018.1466980. Epub. 2018 May 7. PMID: 29668335.
4. Fujimoto S, Kondoh H, Yamamoto Y, Hisanaga S, Tanaka K. Holter electrocardiogram monitoring in nephrotic patients during methylprednisolone pulse therapy. Am J Nephrol. 1990;10(3):231-6. doi: 10.1159/000168087. PMID: 1696428.
5. Marcocci C, Watt T, Altea MA, Rasmussen AK, Feldt-Rasmussen U, Orgiazzi J, Bartalena L; European Group of Graves' Orbitopathy. Fatal and non-fatal adverse events of glucocorticoid therapy for Graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association. Eur J Endocrinol. 2012 Feb;166(2):247-53. doi: 10.1530/EJE-11-0779. Epub. 2011 Nov 4. PMID: 22058081.
6. Vasheghani-Farahani A, Sahraian MA, Darabi L, Aghsaie A, Minagar A. Incidence of various cardiac arrhythmias and conduction disturbances due to high dose intravenous methylprednisolone in patients with multiple sclerosis. J Neurol Sci. 2011 Oct 15;309(1-2):75-8. doi: 10.1016/j.jns.2011.07.018. Epub. 2011 Aug 9. PMID: 21831398.
7. Belmonte MA, Cequiere A, Roig-Escofet D. Severe ventricular arrhythmia after methylprednisolone pulse therapy in rheumatoid arthritis. J Rheumatol [Internet]. 1986 Apr;13(2):477–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3723518.
8. Kumari R, Uppal SS. First report of supraventricular tachycardia after intravenous pulse methylprednisolone therapy, with a brief review of the literature. Rheumatol Int. 2005 Nov;26(1):70-3. doi: 10.1007/s00296-005-0589-7. Epub. 2005 Feb 23. PMID: 15726372.
9. Tvede N, Nielsen LP, Andersen V. Bradycardia after high-dose intravenous methylprednisolone therapy. Scand J Rheumatol. 1986;15(3):302-4. doi: 10.3109/03009748609092597. PMID: 3798047.
10. McLuckie AE, Savage RW. Atrial fibrillation following pulse methylprednisolone therapy in an adult. Chest. 1993 Aug;104(2):622-3. doi: 10.1378/chest.104.2.622. PMID: 8339660.
11. Reddy V, Taha W, Kundumadam S, Khan M. Atrial fibrillation and hyperthyroidism: A literature review. Indian Heart J. 2017 Jul-Aug;69(4):545-550. doi: 10.1016/j.ihj.2017.07.004. Epub. 2017 Jul 5. PMID: 28822529; PMCID: PMC5560908.
12. Yamamura K, Ohga S, Nishiyama K, Doi T, Tsutsumi Y, Ikeda K, Fujishima A, Takada H, Hara T. Recurrent atrial fibrillation after high-dose methylprednisolone therapy in a girl with lupus-associated hemophagocytic syndrome. Lupus. 2011 Jul;20(8):871-5. doi: 10.1177/0961203310392429. Epub. 2011 Mar 17. PMID: 21415254.
13. Cohen IJ. Cardiovascular collapse after high dose methylprednisolone. Pediatr Hematol Oncol. 1993 Jul-Sep;10(3):v-vii. doi: 10.3109/08880019309029486. PMID: 8217535.
14. Schult M, Löhmann D, Knitsch W, Kuse ER, Nashan B. Recurrent cardiocirculatory arrest after kidney transplantation related to intravenous methylprednisolone bolus therapy. Transplantation. 1999 Jun 15;67(11):1497-8. doi: 10.1097/00007890-199906150-00022. PMID: 10385096.
15. Bocanegra TS, Castañeda MO, Espinoza LR, Vasey FB, Germain BF. Sudden death after methylprednisolone pulse therapy. Ann Intern Med. 1981 Jul;95(1):122. doi: 10.7326/0003-4819-95-1-122_1. PMID: 7247116.
16. Miskiewicz P, Milczarek-Banach J, Bednarczuk T, Opolski G, Glowczynska R. Blood Pressure Profile and N-Terminal-proBNP Dynamics in Response to

Intravenous Methylprednisolone Pulse Therapy of Severe Graves' Orbitopathy. Int J Mol Sci. 2018 Sep 26;19(10):2918. doi: 10.3390/ijms19102918. PMID: 30261581; PMCID: PMC6213036.
17. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, Brown JP, Cohen A, Kim H. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013 Aug 15;9(1):30. doi: 10.1186/1710-1492-9-30. PMID: 23947590; PMCID: PMC3765115.
18. Weiss JN, Qu Z, Shivkumar K. Electrophysiology of Hypokalemia and Hyperkalemia. Circ Arrhythm Electrophysiol. 2017 Mar;10(3):e004667. doi: 10.1161/CIRCEP.116.004667. PMID: 28314851; PMCID: PMC5399982.
19. Young SM, Lim AYN, Lang SS, Lee KO, Sundar G. Efficacy and safety of pulsed intravenous methylprednisolone in early active thyroid eye disease. Orbit. 2019 Oct;38(5):362-369. doi: 10.1080/01676830.2018.1553189. Epub. 2018 Dec 12. PMID: 30540214.