Etomidate versus Propofol as Induction Agents in Patients Undergoing Decompressive Procedures for Cervical Compressive Myelopathy with and without Impaired Heart Rate Variability

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Abstract

Background Patients with cervical compressive myelopathy (CCM) are known to have autonomic dysfunction, which can impact surgical outcomes. In such patients, screening patients for heart rate variability (HRV) may enable the anesthesiologist to predict hypotension, thereby attempting to modify the anesthetic technique. This study aimed to compare the hemodynamic changes in CCM patients between propofol and etomidate induction.

Methods Sixty CCM patients aged 18 to 70 years underwent an autonomic function test using HRV before decompressive surgery. The selected patients were randomized into two groups of 30 patients each to receive either etomidate or propofol for induction of anesthesia. The groups were compared for hemodynamic changes, the incidence of pain on injection, and the occurrence of myoclonus. While analyzing the hemodynamic changes, the two groups were subdivided into four groups, namely, propofol group with or without autonomic dysfunction (AD) and etomidate group with or without AD.

Results In the abnormal HRV group, patients induced with propofol showed a significantly higher incidence of hypotension at 3-minute ($p = 0.02$) and 5-minute ($p = 0.04$) time points. On the other hand, in HRV normal patients, induction with propofol showed a significantly higher ($p = 0.03$) incidence of hypotension at 5 minutes. During induction, higher grades of pain ($p = 0.01$) were observed in the propofol group, whereas the occurrence of myoclonus was more in the etomidate group ($p = 0.07$).

Keywords
- cervical compressive myelopathy
- autonomic dysfunction
- heat rate variability
- propofol
- etomidate
- hypotension

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Conclusion As compared with propofol, the use of etomidate in patients with CCM undergoing decompressive procedures reduces hypotensive episodes, more so in patients with impaired HRV. Thus, HRV-based AD categorization may assist in optimal management of postinduction hypotension in patients with CCM.

Introduction

Autonomic dysfunction (AD) is well-recognized after traumatic spinal cord injury; however, very few studies have reported the incidence of AD in cervical compressive myelopathies (CCM).[1,2] Hypotension is the most frequent adverse hemodynamic event noted during the initial intraoperative phase and is frequently linked to poor perioperative outcomes.[3–5] Reduction in arterial blood pressure below the lower limit of the vascular autoregulation curve may result in heart, brain, and kidney ischemia.[3,6] AD has been recognized as one of the variables that assist in predicting postinduction hypotension.[7] Such patients require inotropic support, vasopressors, or other treatments after induction to maintain normotension. Heart rate variability (HRV), the physiological variations of the changes in heartbeats, is a simple objective tool to diagnose AD.[8] It is vital to categorize AD patients preoperatively by performing an objective, easy, and bedside test like HRV and opt for anesthetic agents carefully to avoid the risk of hypotension-induced spinal cord ischemia.[9–11]

Anterior and posterior cervical decompressive procedures are commonly performed neurosurgical procedures for CCM resulting from degenerative or traumatic etiologies.[12] Prevention of hypotension during anesthesia induction is crucial to maintain spinal cord perfusion in these patients with compromised AD. Thus, in patients with CCM, HRV testing may facilitate anesthesiologists to forecast hypotension, thereby optimizing the anesthetic technique for the prevention of hypotension-induced spinal cord ischemia.

Although propofol is the most commonly used induction agent, it is associated with hypotension.[13,14] Etomidate, although a less commonly used agent, has minimal cardiovascular side effects.[15] Etomidate, as an induction agent, reportedly has more cardiovascular stability than propofol in vulnerable patients.[16] However, there are no studies to appraise the suitability of etomidate for induction in patients with impaired AD.

The primary objective of the study was to compare the hemodynamic profile between propofol and etomidate induction in CCM patients requiring decompressive procedures. The incidence of pain on injection and myoclonus were also compared between the two groups as a secondary objective. We hypothesized that etomidate is preferred over propofol for anesthesia induction to minimize hypotension in patients with CCM having AD.

Methods

A single-center, randomized, double-blinded, prospective study conducted from May 2020 to December 2021 included patients with CCM who visited a super specialty care center based in Bengaluru, India. The study was approved by the institutional ethics committee as per the Indian Council of Medical Research (ICMR) guidelines (MSRMC/EC/AP-04/03–2020). Inclusion criteria considered were subjects aged between 18 and 70 years, patients fulfilling American Society of Anesthesiologists (ASA) physical status 1 to 3, and those requiring elective anterior or posterior cervical decompression. The exclusion criteria considered were heart rate or rhythm abnormalities or use of medications known to alter them, sepsis/recovered from sepsis (<6 months), diabetes, degenerative neurological disease (e.g., Parkinson's disease), complete spinal cord injury, and patients requiring re-exploration procedures. This prospective study was registered with Clinical Trials Registry, India before recruitment of cases (CTRI/2021/01/030207). Informed valid written consent was sought from patients in the language comprehensible to them before enrolment.

The sample size was calculated based on a randomized controlled trial in patients undergoing cardiac surgery to assess hemodynamic profiles with etomidate versus propofol,[16] where propofol caused a 34% greater reduction in "MAP (mean arterial pressure)—time integral" from baseline after induction of anesthesia than etomidate ($p < 0.009$). To achieve the power of 90%, a level of significance of 5% (two-sided), and 5% loss to follow-up, our study required a minimum sample size of 30 patients in each group.[16] Patients who underwent HRV testing were randomized to the etomidate and propofol groups in the ratio of 1:1 based on computer-generated random allocation after obtaining informed consent. As per the random allocation number, the clinicians involved in the trial induced the patients with etomidate or propofol.

The HRV testing for autonomic function was performed using Vagus HRV (Recorders and Medicare Systems-RMS, India) a day before surgery. The patients were made to rest in the supine position for 10 minutes. Electrocardiographic (ECG) leads were connected as per standards, and lead II ECG was recorded continuously for 10 minutes with the patients' eyes open. The data were extracted using Vagus HRV apparatus. The ECG was analyzed using RMS Vagus HRV software (RMS, India). Time-domain parameters measured were standard deviation of NN (the number of RR interval differences) intervals (SDNN ms), root mean square of successive RR interval differences (RMSSD ms), and percentage of successive RR intervals that differ by >50 ms (pNN50%). Frequency-domain variables measured were low-frequency (LF) power in ms^2 (0.04–0.15 Hz), high-frequency (HF) power in ms^2 (0.15–0.4 Hz), total power (ms^2), and the ratio of LF to HF power (LF/HF%).

The HRV-based classification into normal and abnormal groups was done based on HRV metrics and norms (►**Fig. 1**).[17] The current study majorly considered the

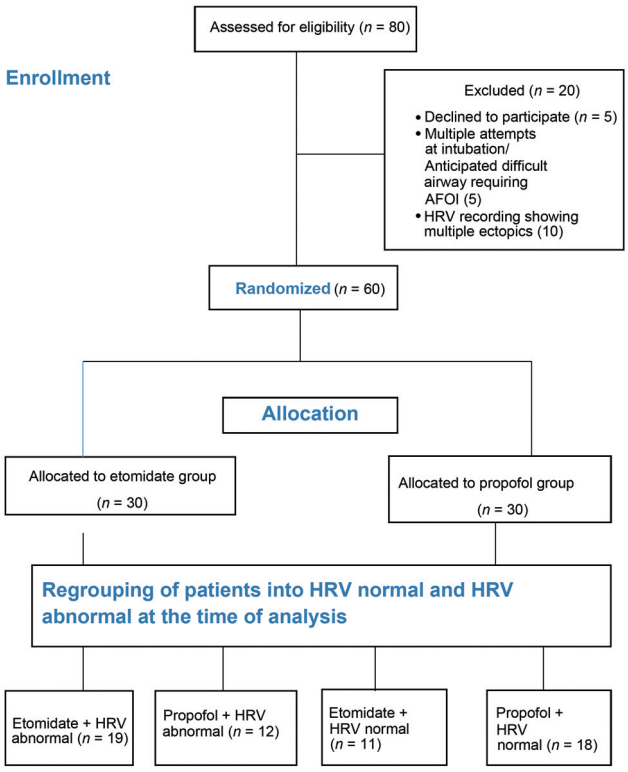

Fig. 1 CONSORT 2010 diagram depicting the patient enrolment and subgrouping.

LF/HF ratio as an indicator of sympathovagal balance. Therefore, short-term recordings of 10 minutes were conducted, and 1.1 was considered the cutoff value between normal and deviated LF/HF ratio. Statistical analysis was done based on LF/HF ratio >1.1 to 11.6 (normal HRV) and LF/HF ratio <1.1 (abnormal HRV).[17] While analyzing the hemodynamic data, the two groups were subdivided into four groups, namely, the propofol group with or without AD and the etomidate group with or without AD based on HRV.

On the day of surgery, all subjects received 500 mL of Ringer's lactate in the preoperative room before shifting to the operation room. ASA standard monitors were connected before induction. After lignocaine infiltration, radial artery was cannulated for invasive blood pressure monitoring with a 20-gauge cannula under ultrasound guidance. Baseline values were recorded, and preoxygenation was done for 3 minutes. The etomidate group received intravenous (IV) fentanyl 2 µg/kg, etomidate 0.3 mg/kg, vecuronium 0.1 mg/kg, followed by tracheal intubation and intermittent positive pressure ventilation (IPPV) with oxygen, nitrous oxide, and sevoflurane to achieve minimum alveolar concentration (MAC) 1.0. The propofol group received propofol 2 mg/kg, and the rest of the protocol remained the same. Both induction agents were administered over a period of 30 to 60 seconds. A propofol preparation of 1% emulsion with a combination of medium chain triglyceride (MCT) and long chain triglyceride (LCT) and etomidate of 0.2% emulsion containing MCT were used for induction.

The heart rate and invasive blood pressures were continuously recorded and noted at preinduction, postinduction, laryngoscopy, and 1, 3, 5, 10, and 15 minutes postintubation (PI). Occurrence of pain at injection and any myoclonic movements were also recorded. Hypotension, defined as a reduction in MAP <60 mm Hg or 20% of baseline, was treated with ephedrine 6 mg IV bolus. The ephedrine boluses were repeated if the hypotension did not settle in 60 seconds. Patients with bradycardia (<50 beats per minute) received atropine 0.6 mg IV. Total ephedrine and atropine used were noted, and adverse effects were carefully monitored. Pain on injection was recorded on a 4-grade scale, with 0 = no pain, 1 = verbal complaint of pain, 2 = withdrawal of the arm, and 3 = both verbal complaint and withdrawal. Myoclonus in patients was recorded on a scale of 0 to 2 (0 = no myoclonus, 1 = minor myoclonus movement, and 2 = major myoclonus). While analyzing the data, the patients were subgrouped as the etomidate group with normal preoperative HRV, etomidate group with impaired preoperative HRV, propofol group with normal preoperative HRV, and propofol group with impaired preoperative HRV. Intraoperative drop in blood pressure at different time intervals after induction and total usage of vasopressors to treat this hypotension was recorded. The data were collected till MAP returned to normal or till 15 minutes postinduction or whichever was longer.

Statistical analysis: Descriptive and inferential statistical analyses were performed. Continuous variables were presented as mean ± SD (minimum–maximum) and categorical variables as percentages. Significance was assessed at a 5% level of significance. The following two assumptions on data were made, that is, dependent variables should be normally distributed and two samples drawn from the population were random. Independent Student's *t*-test (two-tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups (intergroup analysis) on metric parameters. Chi-squared/-Fisher's exact test was used to find the significance of the study parameters on a categorical scale between two or more groups in a nonparametric setting for qualitative data analysis. VassarStats online tools were used for all the statistical computation, and the line graphs were plotted using Excel 2019. Cramér's V effect was used to find the effect size. Since the sample size was <30 for each subgroup, a nonparametric test was used for the comparison.

Results

Out of 80 patients initially evaluated for enrolment eligibility, 20 were excluded before allotment due to various reasons (anticipated difficult airway requiring awake fiberoptic intubation [AFOI], multiple ectopics noted during HRV recording, refusal to consent after HRV recording, etc.). The 60 selected patients were randomized into two groups using a computer-generated list (100 numbers with a block of 5) of 30 each to receive either etomidate or propofol. The anesthetists attending the cases were blinded to HRV parameters and analysis. The CONSORT 2010 diagram depicting the patient enrolment and subgrouping (etomidate with normal and abnormal HRV and propofol with normal and abnormal HRV) is shown in ►**Fig. 1**.

Table 1 Demographic and diagnostic details between etomidate and propofol group

(*N* = 60)	Etomidate (*N* = 30)			Propofol (*N* = 30)		
	HRV normal (*N* = 11)	HRV abnormal (*N* = 19)	*p*-value	HRV normal (*N* = 18)	HRV abnormal (*N* = 12)	*p*-value
Age	51.0 ± 17.13	45.84 ± 16.15	0.42	47.39 ± 16.54	48.75 ± 12	0.81
Gender (M/F)	7/4	10/9	0.25	11/7	4/8	0.60
Height	161.46 + 6.8	161.79 + 11.05	0.93	161.44 + 9.49	160.75 + 10.40	0.85
BMI	24.98 + 2.31	24.48 + 1.40	0.46	25.58 + 1.78	23.97 + 1.18	0.07
Spondylosis with canal stenosis	3 (27.27%)	10 (52.63%)	0.18	2 (11.11%)	7 (58.33%)	0.002
OPLL with compression	6 (54.5%)	3 (15.78%)	0.02	5 (27.77%)	3 (25%)	0.45
Spondylolisthesis with compression	2 (18.18%)	631.57%)	0.43	11 (61.11%)	2 (16.66%)	0.07
Levels of compression						
2–4	5 (45.45%)	9 (47.36%)	0.91	10 (55.55%)	6 (50%)	0.78
4–6	6 (54.54%)	10 (52.63%)	0.915	8 (44.44%)	6 (50%)	0.58

Abbreviations: BMI, body mass index; HRV, heart rate variability; OPLL, ossified posterior longitudinal ligament.
Note: Data expressed as mean + standard deviation and *n* (%).

The demographic and the diagnostic variables between etomidate and propofol groups are shown in ►**Table 1**. The age, gender, height, and body mass index (BMI) were comparable between the groups. The patients with spondylosis with canal stenosis were higher in the abnormal HRV group, and it was significant in abnormal HRV group who received propofol ($p = 0.002$). The details of time and frequency domains of HRV between etomidate and propofol groups are listed in ►**Table 2**. The corresponding number of patients noted with abnormal SDNN (ms), RMSSD (ms), NN50, total power (ms^2), low-frequency power (ms^2), high-frequency power (ms^2), and LF/HF ratio on HRV analysis were 51 (85.0%), 41 (68.33%), 40 (66.66%), 35 (58.33%), 40 (66.66%), 43 (71.66%), and 31 (51.67%), respectively.

Heart rate changes were similar in all the groups and were not statistically significant. Based on the HRV (LF/HF) analysis and the blood pressure response, the patients were analyzed after subgrouping them into CCM patients with AD ($n = 31$, of which 19 received etomidate and 12 received propofol) and CCM patients without AD ($n = 29$, of which 11 received etomidate and 18 received propofol). Hypotensive episodes at 1, 3, 5, and 10 minutes were observed to be higher in the propofol group compared with the etomidate group in patients both with and without AD. The episodes of hypotension were observed to be higher at postintubation 3 ($p = 0.02$), 5 ($p = 0.04$), and 10 (0.06) minutes in propofol with AD group and at postintubation 5 minutes in propofol without AD (►**Fig. 2**). The observed effect size was 0.26, 0.37, and 0.056 for comparison of hypotension in the abnormal HRV group at 3, 5, and 10 minutes, respectively. This indicates that the magnitude of the difference between the observed data and the expected data was medium at 3 and 5 minutes, whereas at the 10th minute, the difference was very minimal.

Hypotensive episodes at various time points were significantly higher in patients with abnormal HRV than in patients with normal HRV, requiring significantly higher doses of ephedrine (►**Figs. 3** and **4**). Comparative analysis of pain and myoclonus between the two groups demonstrated that the etomidate group had lower grades of pain than propofol. The result was statistically significant (►**Table 3**), and myoclonus was noted higher in the etomidate group.

Discussion

The pathogenesis of CCM involves compression of the cervical spinal cord resulting in dysfunction of ascending and descending tracts and spinal gray matter, causing motor, sensory, and autonomic disturbances like bladder, bowel, and sexual dysfunctions. There is a sparsity of literature on the incidence of cardiac AD in CCM patients although it is well documented in traumatic spinal cord pathologies.[1] We assessed AD with various time- and frequency-domain HRV parameters. AD was observed in 51.67% of patients when deviated LF/HF ratio was considered to define abnormal HRV as in our study in CCM patients requiring decompression.

According to the Task Force of the European Society of Cardiology and the North American Society of Pacing and

Table 2 Heart rate variability (HRV) in etomidate and propofol group

HRV variables	Etomidate (mean ± SD)	Propofol (mean ± SD)	*p*-value
SDNN (ms)	150.03 ± 69.48	147.19 ± 58.97	0.38
RMSSD (ms)	85.10 ± 128.26	79.22 ± 106.27	0.38
NN50 (ms)	11.16 ± 4.20	9.62 ± 3.70	0.21
Total power (ms^2)	2,121.05 ± 1,315.76	2,606.38 ± 1,120.75	0.13
Low-frequency power (ms^2)	945.12 ± 597.86	954.45 ± 679.21	0.48
High-frequency power (ms^2)	932.28 ± 1,068.94	843.79 ± 450.16	0.34
LF/HF ratio	1.10 ± 0.34	1.21 ± 0.80	0.12

Abbreviations: HF, low frequency; HF, high frequency; NN50, successive RR intervals that differ by >50 ms; RMSSD, root mean square of successive RR interval differences; SDDN, standard deviation of NN intervals;

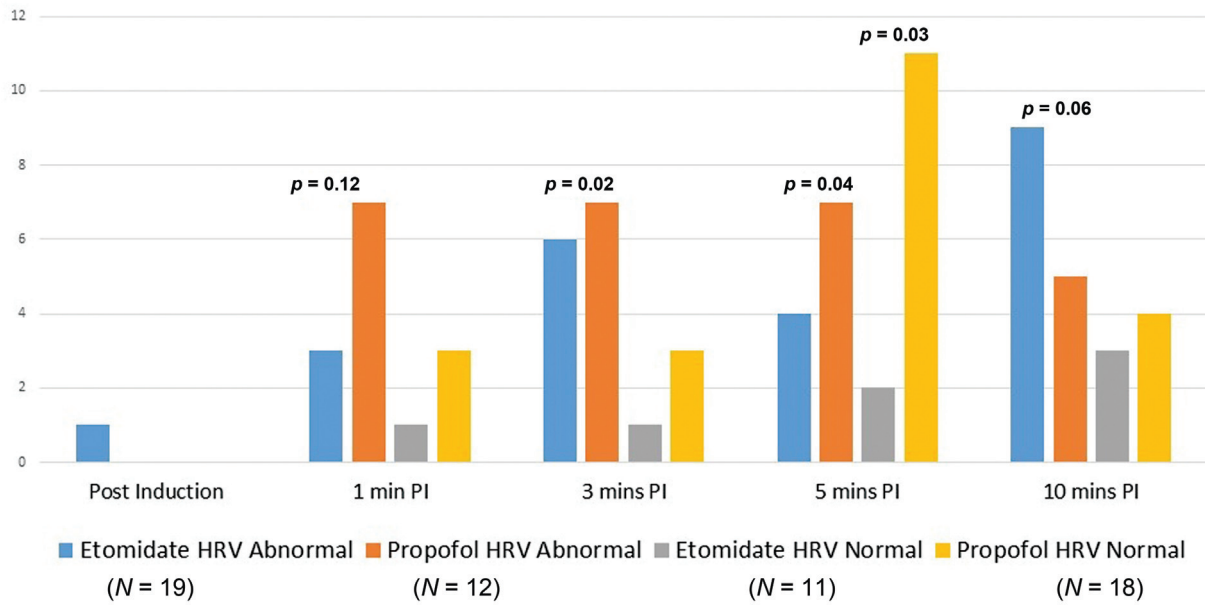

Fig. 2 Comparative analysis of hypotensive episodes among the groups.

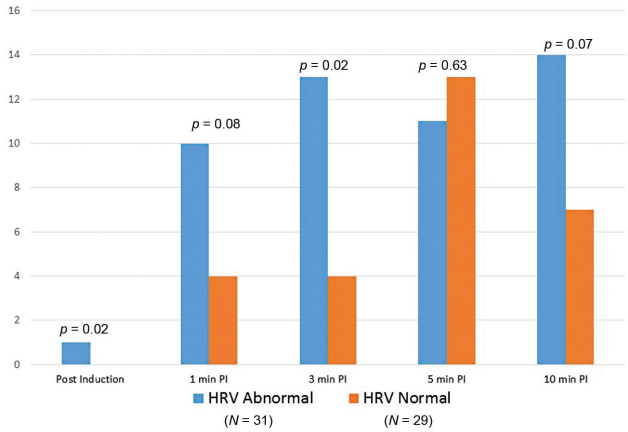

Fig. 3 Comparative analysis of hypotensive episodes between heart rate variability (HRV) abnormal and HRV normal groups.

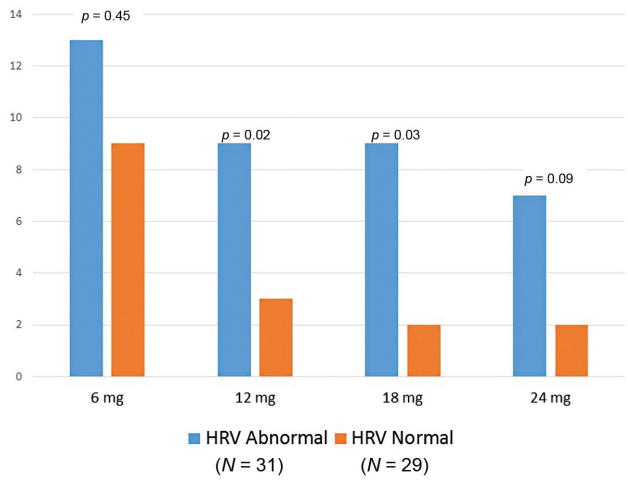

Fig. 4 Comparative analysis of ephedrine requirement between heart rate variability (HRV) abnormal and HRV normal groups.

Table 3 Comparative analysis of pain and myoclonus with induction anesthesia

		Etomidate ($n = 30$)	Propofol ($n = 30$)	p-value
Pain on injection	No pain	18 (60.0%)	12 (40.0%)	0.21[a]
	Verbal complaint of pain	12 (40.0%)	10 (33.33%)	0.07[a]
	Withdrawal of arm	0	8 (26.67%)	0.01[b]
Myoclonus	No myoclonus	23 (76.67%)	28 (93.33%)	0.07[b]
	Minor myoclonus movement	7 (23.33%)	2 (6.67%)	

[a]Chi-squared test.
[b]Fisher's exact test.

Electrophysiology (1996), analysis of short-term HRV recordings (5 minutes) is generally used to evaluate the pathophysiological correlation of autonomic control with HRV.[18] Studies have noted vagal activity as a key contributor to the HF component.[19] Certain investigators have used LF/HF ratio to mirror sympathovagal balance or to reflect sympathetic modulations. Hence, HRV is considered standard for the diagnosis/classification of parasympathetic and sympathetic responses. RMS Vagus HRV software used in the current study is a validated and standard tool for noninvasive testing of AD.[19] The study has primarily evaluated the LF/HF ratio, which mirrors both the components of autonomic function.

The cardiac autonomic system plays an important role in the occurrence of hypotension after induction of anesthesia in patients undergoing elective surgery.[17] The present study has evaluated the potential of HRV in predicting hypotensive CCM patients during decompressive surgery and the superiority of etomidate over propofol in preventing postinduction hypotension. The study has found that patients who encountered hypotension postinduction ($p = 0.02$) and postintubation at 1 minute ($p = 0.08$), 3 minutes ($p = 0.02$), and 10 minutes ($p = 0.07$) were more among patients with AD compared with those without AD. In addition, the ephedrine requirement was significantly higher in patients diagnosed with AD than in those without AD.

Our study found that the patients with canal stenosis secondary to cervical spondylosis had significantly abnormal HRV recordings ($p = 0.003$) as compared with patients diagnosed with OPLL and spondylolisthesis causing cord compression. A study by Shindo et al reported the presence of AD in CCM secondary to cervical spondylosis. This study group measured muscle sympathetic nerve activity (MSNA), an indicator of sympathetic outflow to muscles, which was found to be significantly reduced in patients with cervical spondylosis. The authors attributed the negative correlation between burst incidence of MSNA and motor power to the posterior column involvement.[20]

The current study has shown that HRV-based AD categorization may help better predict postinduction hypotension. Several previous studies have analyzed the clinical use of HRV in predicting hypotension.[21–23] Hanss et al studied HRV-directed severe hypotension in patients scheduled to undergo elective cesarean delivery. They found that LF/HF is a useful tool to suggest prophylactic therapy in patients at risk of hypotension after a subarachnoid block during cesarean delivery.[21] In line with this finding, the present study has shown that a lower LF/HF ratio is an indicator of sympathovagal imbalance. In a study on patients with human T-lymphotropic virus type 1 (HTLV-1) associated myelopathy, the LF/HF ratio was found to be an indicator of sympathovagal balance. This group demonstrated that the LF/HF ratio was further reduced in patients with orthostatic hypotension, and it also correlated with cord atrophy on imaging.[24]

Etomidate is not as commonly used as propofol for induction of anesthesia for various reasons. The incidence of myoclonus has been reported as much as 50 to 80% after etomidate induction,[25] and there is a high rate of transient adrenal insufficiency and mortality, especially in patients with sepsis, which is debatable.[26,27] But etomidate has a favorable hemodynamic profile due to its unique lack of effect on both the sympathetic nervous system and baroreceptor function[28,29] and its capacity to bind and stimulate peripheral α-2B adrenergic receptors with subsequent vasoconstriction.[30] Hypotension occurring with propofol is mainly due to the reduction of sympathetic activity causing vasodilation or its direct effect on vascular smooth muscles and myocardial depression.[31,32]

Various authors have studied the effects of propofol and etomidate on the autonomic nervous system (ANS) objectively. Wang et al studied a spectrogram derived by continuous wavelet transform of electrocardiography and pulse photoplethysmography (PPG) signals at baseline, early phase, and late phase after propofol induction. They found that propofol administration resulted in reductions in instantaneous high frequency (HFi) and low frequency (LFi) and increases in the LFi/HFi ratio and PPG amplitude. This study demonstrated significant immediate changes in ANS activity that include temporally relative elevation of cardiac sympathovagal balance and reduced sympathetic activity after propofol.[33] Ebert et al studied changes in MSNA, forearm vascular resistance, and blood pressure after propofol and etomidate administration. MSNA was reduced after propofol leading to a reduction in forearm vascular resistance and significant hypotension, whereas etomidate preserved these. Both cardiac and sympathetic bar slopes were maintained with etomidate but were significantly reduced with propofol, especially in response to hypotension.[34] The current study administered HRV testing

preoperatively to all CCM patients requiring decompression and found etomidate administration prevented postinduction hypotension better as compared with propofol, especially in patients with abnormal preoperative HRV. However, we did not perform HRV testing during or after the administration of these induction agents.

Several studies have compared the effectiveness of etomidate over propofol in preventing perioperative hypotension.[16,35,36] Comparison of the efficacy of etomidate over propofol in cardiac surgical patients by Ladha et al showed that the adrenal suppression caused by etomidate can present a challenge to the anesthesiologist in a variety of clinical settings, despite its superior hemodynamic profile.[36] This finding is debatable, but the present study has excluded patients who could have had adrenal suppression. Although not statistically significant, the overall pain score was more in the propofol group and increased incidence of myoclonus in the etomidate group. Several Indian studies have reported similar findings.[37–39]

The present study holds significant relevance, as there is very limited literature evidence suggesting the potential of preoperative HRV in detecting AD in CCM patients. In addition, the study has also highlighted the potential benefit of etomidate in reducing the incidence of hypotension on induction in CCM patients with impaired HRV.

One of the major limitations of the current study is the single-center study design. The number of patients belonging to each group was further reduced due to the categorization of etomidate and propofol groups into HRV normal and HRV abnormal groups. Hence, the power of the study calculated retrospectively was low (0.53). The correlation of preoperative neurological deficits and chronicity of CCM with HRV analysis would give valuable information. Large-scale, multicenter, randomized clinical trials are warranted to corroborate.

Conclusion

We conclude that HRV-based AD categorization of CCM patients may assist in better prediction of postinduction hypotension, and etomidate is preferred over propofol for induction of anesthesia in these patients. Pain scores were higher following propofol injection, and myoclonus incidence was higher after etomidate induction.

Conflict of Interest
None declared.

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