Original Article

Prevalence and predictors of preoperative cardiac autonomic dysfunction among elective neurosurgical patients: A prospective observational study

RP Sangeetha, Dhritiman Chakrabarti, Kamath Sriganesh, Musumur Mahendranath, Sathyaprabha TN[1], Dwarakanath Srinivas[2]

Departments of Neuroanesthesia and Neurocritical Care, [1]Neurophysiology and [2]Neurosurgery, NIMHANS, Bangalore, Karnataka, India

Address for correspondence: Dr. Kamath Sriganesh, Department of Neuroanaesthesia and Neurocritical Care, Neurosciences Faculty Block, 3rd Floor, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore – 560 029, Karnataka, India. E-mail: drsri23@gmail.com

Submitted: 28-Jul-2023
Revised: 24-Jan-2024
Accepted: 26-Jan-2024
Published: 13-Mar-2024

Access this article online

Website: https://journals.lww.com/ijaweb

DOI: 10.4103/ija.ija_722_23

Quick response code

ABSTRACT

Background and Aims: The autonomic nervous system (ANS) is cardinal for systemic homeostasis. Autonomic dysfunction is prevalent in as high as 65% of patients presenting for cardiac surgery in the Indian scenario. Pre-existing cardiac autonomic dysfunction (CAD) in surgical patients can accentuate perioperative haemodynamic fluctuations during stressful intraoperative events, predispose to adverse cardiac events, and contribute to morbidity and mortality. The prevalence and predictors of CAD in the elective neurosurgical population are unknown in the Indian scenario. The current study was conducted to bridge this knowledge gap. **Methods:** In this single-centre prospective observational study conducted at a tertiary care neurosciences centre, among 400 consenting adult patients of either gender, between 18 and 80 years of age, undergoing elective neurosurgery, the preoperative ANS function at the bedside was assessed as the primary outcome measure. The ANS status was evaluated using ANSiscope™-derived indices of heart rate variability. The diagnosis of CAD was made when the ANS index exceeded a threshold of 13.5. Data regarding predictors of CAD were collected from patient records as the secondary outcome measure. Statistical analysis was done using the R software. A *P*-value of <0.05 was considered statistically significant. **Results:** The prevalence of preoperative CAD in our study population was 79.7% (319/400 patients). None of the demographic and baseline clinical characteristics we studied predicted CAD in our study. **Conclusion:** We observed a significant prevalence of preoperative CAD among elective neurosurgical patients. None of the parameters we evaluated predicted CAD in our study.

Keywords: Dysautonomia, neurosurgery, perioperative, prevalence

INTRODUCTION

The autonomic nervous system (ANS) is crucial for maintaining systemic homeostasis. The integrity of the sympathetic and parasympathetic components is important for regulating and modulating cardiovascular, respiratory, haemodynamic, gastrointestinal, and thermoregulatory functions. About 1/1000 population hospitalised in the United States are affected by pathological perturbations of the ANS in the form of orthostatic intolerance syndromes secondary to cardiac autonomic dysfunction (CAD).[1]

When patients with CAD present for surgical procedures, they may manifest severe haemodynamic responses that may be less responsive to pharmacological interventions. Pre-existing CAD can accentuate perioperative haemodynamic fluctuations during stressful events such as direct laryngoscopy,

How to cite this article: Sangeetha RP, Chakrabarti D, Sriganesh K, Mahendranath M, Sathyaprabha TN, Srinivas D. Prevalence and predictors of preoperative cardiac autonomic dysfunction among elective neurosurgical patients: A prospective observational study. Indian J Anaesth 2024;68:380-6.

endotracheal intubation, and extubation and result in major adverse cardiac events (MACEs). The complications arising from CAD can prolong the duration of hospital stay and contribute to significant patient morbidity and mortality.[2] The anatomical location of the key autonomic regulatory structures within the central nervous system predisposes to secondary CAD among patients with intracranial pathologies, especially after direct neurosurgical handling.[3]

Real-time heart rate variability (HRV) assessment using the ANSiscope™ equipment informs about the sympathovagal balance. Previous studies have demonstrated this device's validity[4] and utility in the perioperative period during electroconvulsive therapies,[5] cervical spine,[6] intracranial[7] cardiac,[8] and obstetric surgeries.[9]

The primary aim of this study was to assess the prevalence of CAD in the immediate preoperative period in patients undergoing elective neurosurgical procedures. Our secondary objective was to identify potential predictors of CAD in the neurosurgical population. We hypothesised that the prevalence of CAD will be higher in neurosurgical patients due to the intricate relationship between the pathological brain and ANS.

METHODS

This was a prospective observational study from a tertiary neurosciences academic hospital. The institute ethics committee approval was obtained [NIMHANS/33 IEC (BS and NS DIV)/2021, dated 17 December 2021], and the study was registered with Clinical Trials Registry-India (ID: NCT05230641; clinicaltrials.gov). Consenting patients scheduled for elective neurosurgical procedures at our centre from May 2022 to April 2023 were recruited if they fulfilled the study inclusion criteria. We included patients who were aged ≥18 years, belonged to the American Society of Anesthesiologists (ASA) physical status 1–4, and were scheduled for elective craniotomies or spine surgeries under general anaesthesia. We excluded patients undergoing emergency procedures or awake craniotomies, patients with preoperative cardiac failure or arrhythmias, and patients on preoperative vasopressor or inotropic support. The study was conducted in accordance with the principles of the Declaration of Helsinki, 2013. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. Demographic and baseline clinical data, including co-morbid conditions, were collected. The ANS function was assessed using the ANSiscope™ device (Dyansys Inc., Burlingame, CA, United States) in the preoperative period, before the induction of anaesthesia, to identify the prevalence of CAD in the elective neurosurgical population. Data regarding potential risk factors such as age, gender, body mass index (BMI), socio-economic status (SES), educational qualification, occupation, pre-existing co-morbidities [hypertension, diabetes mellitus (DM), ischaemic heart disease (IHD)], ASA physical status, and the diagnosis of neurosurgical pathologies were collected. The presence of preoperative pain and anxiety was assessed using a numerical rating scale (NRS) score (0–10), with 0 implying no pain or anxiety and 10 indicating significant pain or anxiety.

We opted for a simple bedside assessment tool to cater to our neurosurgical patients who commonly present with neurological defects and altered sensorium that renders them unsuitable for the conventional method of ANS testing. The ANSiscope™ device works on the principle of scale covariance physics. This device is similar to a portable electrocardiography (ECG) device used to record cardiac electrical activity. The inbuilt algorithm analyses 572 consecutive R-R intervals of the ECG and creates two unique scalar imprints for the sympathetic and parasympathetic systems. Based on the degree of the inter-scalar discordance, it computes the ANS index (0–100) to diagnose (ANS index >13.5) and quantify the degree of CAD, with increasing values suggesting greater abnormal sympathetic dominance and CAD severity. Figure 1 shows the parameters displayed by the ANSiscope™ monitor. We diagnosed CAD in our patients based on an ANS index of >13.5.[8]

Figure 1: Heart rate variability parameters displayed by the ANSiscope™

Previous studies in the non-neurosurgical population have determined the prevalence of CAD to vary from 25% to 73%.[9,10] Considering an average prevalence of CAD of 50% in the neurosurgical population and a possible 5% margin of error, a sample size of 383 was deemed necessary for achieving a 95% confidence level.[10] Hence, we inflated the sample size to 400 patients to account for the potential loss of data from any cause.

The collected data were analysed using R software ver 4.1.2. Interval scale data are presented as medians and interquartile ranges, and nominal variables are presented as frequencies and percentages. Univariate analysis for the prediction of CAD was conducted using Firth's Bias-Reduced binary logistic regression (package 'logistf'). The effect is presented as odds ratios with 95% confidence intervals. A *P*-value of <0.05 was considered statistically significant.

RESULTS

We screened 470 patients scheduled for elective neurosurgical procedures during the 1 year for possible inclusion into the study. After the exclusion of 40 patients for various reasons, 430 patients were recruited into the study [Figure 2]. The final data analysis was performed for 400 patients.

The demographic characteristics (gender, BMI, SES, education, occupation, and co-morbid status) and baseline clinical characteristics (anxiety, pain, neurosurgical diagnosis, and ASA physical status) [Tables 1 and 2] were comparable among those who were diagnosed with CAD and those who had a normal ANS. The most common surgeries performed on our study patients were for supratentorial (37.9%) pathologies, followed by vascular pathologies (13.48%) and seller pathologies (12.5%) [Table 3]. The median (interquartile range) age of our study population was 42 (32–53) years, and 57% were males [Table 1]. The CAD prevalence in our study cohort was 79.7% (319/400 patients) based on an ANS index threshold of >13.5. Among those with CAD, 39% (156/400 patients) had early CAD (ANS index between 13.5 and 24.9), 32% (128/400 patients) had late CAD (ANS index between 25 and 50), and 8.7% (35/400 patients) had advanced CAD (ANS index between 50 and 100). The pre-existing co-morbidities in our study population included DM (16%), hypertension (17.2%), IHD (1.2%), and others, including thyroid dysfunction (12.5%). The median preoperative pain and anxiety scores among our patients were 0 (no pain or anxiety) and were not different between those with and without CAD.

DISCUSSION

This prospective study unveiled a significant burden of CAD as 79.7% of the recruited 400 patients based on an ANS index above 13.5.

The ANS assessment is traditionally performed using the conventional Ewings battery of ANS functional tests for sympathetic and parasympathetic systems, which evaluate the patient's haemodynamic response to different dynamic and provocative manoeuvres. The HRV-based ANS assessment involves time, frequency, and non-linear domains of analysis of the ECG tracings. We used a simple bedside HRV-based monitor to study the ANS functional integrity.

The reported prevalence rates for CAD among surgical patients vary widely between 1% and 90%[2] due to

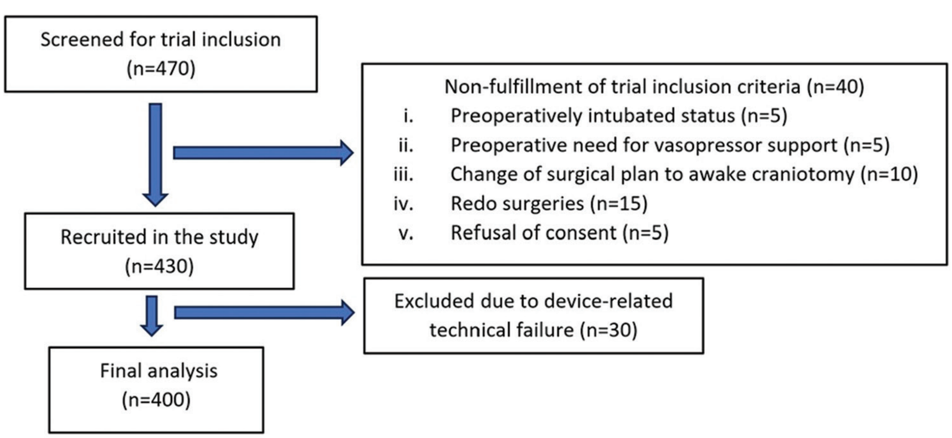

Figure 2: Schematic representation of patient inflow into the study

Table 1: Demographic and baseline clinical characteristics of the study population

Demographic parameters	Overall (*n*=400)	CAD (*n*=319)	No CAD (*n*=81)	OR (95% CI)	*P*
Age (years)	42 (32–53)	42 (32–53)	43 (31–49.5)	1 (0.98, 1.02)	0.957
Body mass Index (kg/m^2)	22.8 (20.4–25.2)	22.75 (20.4–25.2)	23.24 (21.1–25.2)	0.98 (0.91, 1.05)	0.51
ASA physical status	1 (1–2)	1 (1–2)	1 (1–2)	0.94 (0.72, 1.38)	0.714
NRS for preoperative pain	0 (0–1)	0 (0–1)	0 (0–2)	0.93 (0.83, 1.07)	0.298
Preoperative NRS-A	0 (0–10)	0 (0–10)	0 (0-10)	1 (0.98, 1.01)	0.48
ANS index	20.5 (15–33)	24 (17–35)	10 (8–11)	1.54 (1.28, 2.13)	<0.001

Data expressed as median (interquartile range) or Odds ratio (95% confidence interval). ASA: American Society of Anesthesiologists, NRS: numerical rating scale, NRS-A: numerical rating scale for anxiety, CAD: cardiac autonomic dysfunction, OR: odds ratio, CI: confidence interval, ANS: autonomic nervous system

Table 2: Relationship between demographic variables and cardiac autonomic dysfunction

Demographic characteristics	CAD present (*n*=319)	CAD absent (*n*=81)	OR (95% CI)	*P*
Gender				
Female	136 (42.6%)	36 (44.4%)	-	-
Male	183 (57.3%)	45 (55.5%)	1 (0.58, 1.71)	0.991
Socio-economic status				
Intermediate	84 (26.3%)	26 (32%)	0.81 (0.45, 1.49)	0.495
Above Poverty Line	192 (60.1%)	42 (51.8%)	-	-
Below Poverty Line	43 (13.4%)	13 (16%)	1.21 (0.55, 3.03)	0.649
Education				
Illiterate	43 (13.4%)	13 (16%)	0.92 (0.3, 2.69)	0.873
Primary	170 (53.2%)	39 (48.1%)	0.9 (0.33, 2.12)	0.819
Secondary	72 (22.5%)	16 (19.7%)	1.12 (0.38, 3.06)	0.829
Graduate	30 (9%)	10 (12.3%)	-	-
Postgraduate	4 (1.2%)	3 (3%)	0.67 (0.11, 7.32)	0.702
Domicile				
Rural	144 (45.1%)	42 (51.8%)	-	-
Urban	175 (54.8%)	39 (48.1%)	1.32 (0.77, 2.26)	0.309
Occupation				
Business	16 (5%)	3 (3.7%)	-	-
Daily Wage Worker	70 (21.9%)	26 (32%)	0.42 (0.08, 1.47)	0.19
Employee	86 (26.9%)	17 (20.9%)	0.88 (0.16, 3.27)	0.864
Farmer	56 (17.5%)	17 (20.9%)	0.6 (0.11, 2.24)	0.471
Other	91 (28.5%)	18 (22.2%)	0.68 (0.13, 2.44)	0.585
Co-morbid illness				
Diabetes mellitus	51 (15.9%)	15 (18.5%)	0.67 (0.35, 1.36)	0.257
Hypertension	55 (17.2%)	19 (23.4%)	0.57 (0.31, 1.09)	0.085
Ischaemic Heart Disease	4 (1.2%)	1 (1.2%)	0.56 (0.1, 5.68)	0.565
Other (thyroid illness, epilepsy)	40 (12.5%)	9 (11.1%)	1.2 (0.53, 3.16)	0.672

Data expressed as numbers (percentages). CAD: Cardiac autonomic dysfunction, OR: odds ratio, CI: confidence interval, '-': Reference category of the predictor variable

the differences in study population, methodology and equipment used, and definition of CAD diagnosis. Based on non-cardiac autonomic reactivity to an orthostatic load, Reimer *et al*.[11] reported a preoperative CAD prevalence rate of 56% (30/53) in patients who underwent major abdominal surgery. The CAD was diagnosed in 68/108 (62%) parturients undergoing caesarean section surgery based on an ANS index above 21.[9] The ANS index was reported to be >13.5 among 65% of cardiac surgical patients.[8] Based on the HRV parameters, Polderman *et al*.[12] reported a 68% prevalence of CAD among 82 patients who underwent major abdominal and cardiac surgeries.

In the absence of precedent studies among neurosurgical patients, the CAD prevalence based on the ANS index observed in our study was greater than that reported in non-neurosurgical patients undergoing abdominal and cardiac surgeries.[12] Our patient's demographic parameters (age, gender, SES, educational qualification, occupation, BMI, and co-morbid status) were evaluated to explore their contribution to preoperative CAD. Parashar *et al*.[13] and Abhishekh *et al*.[14] observed an overall reduction in cardiac autonomic control with increasing age due to an exaggerated sympathetic tone and a diminished vagal tone. However, we did not observe an association between age and CAD. This could be due to a minimal

Table 3: Relationship between surgical characteristics and cardiac autonomic dysfunction based on ANS index

Nature of Surgery	Categories	CAD present (*n*=319)	CAD absent (*n*=81)	OR (95% CI)	*P*
Location	Cranial	258 (76.5%)	50 (79.3%)	-	-
	Non-cranial non-spinal	5 (1.4%)	0 (0%)	2.15 (0.24, 283.76)	0.568
	Spine	74 (21.9%)	13 (20.6%)	1.08 (0.58, 2.14)	0.821
Location Details	Cervical Spine	33 (9.7%)	5 (7.9%)	-	-
	Cerebello-Pontine Angle	26 (7.7%)	10 (15.8%)	0.41 (0.12, 1.27)	0.125
	Epilepsy	5 (1.4%)	0 (0%)	1.81 (0.16, 249.53)	0.683
	Infratentorial	15 (4.4%)	6 (9.5%)	0.39 (0.1, 1.42)	0.152
	Peripheral nerve	4 (1.1%)	0 (0%)	1.48 (0.13, 206.09)	0.794
	Sella	42 (12.4%)	5 (7.94%)	1.27 (0.35, 4.63)	0.713
	Non-cervical spine	41 (12.1%)	8 (12%)	0.8 (0.24, 2.53)	0.708
	Supratentorial	125 (37%)	24 (38.1%)	0.84 (0.28, 2.15)	0.731
	Vascular	46 (13.6%)	5 (7.9%)	1.39 (0.38, 5.05)	0.611

CAD: cardiac autonomic dysfunction, OR: odds ratio, CI: confidence interval, '-':-Reference category of predictor variable, ANS: Autonomic nervous system

representation of extremes of age in our study population, where derangements of ANS are known to predominate. Moodithaya *et al*.[15] and Ramaekers *et al*.[16] observed that adolescent and adult female participants exhibit a parasympathetic predominance and lower sympathetic activity, acknowledging the possible role of gender hormones in ANS modulation. In our study, there were no gender predispositions among patients who developed CAD, akin to the observation of Zafar *et al*.[17]

The Whitehall II study observed an age-adjusted prevalence of low-mean low-frequency power and HRV among participants with low employment grades.[18] In a study by Sloan *et al*.[19], participants with high-school to college and post-college education had 26% and 43% greater LF R-R variability, respectively, compared to those with less than a high school education. These studies demonstrate the impact of socio-economic disparities on the development of psychosocial stress proportional to their rank of inferiority, thus contributing to impaired parasympathetic regulation and CAD. This observation contrasts with our study, where we did not find a predictive role for education, occupation, and SES on CAD.

CAD has been implicated in the pathophysiology of cardiovascular complications among the obese.[20] The ANS profile in the obese is characterised by parasympathetic activity reduction with a relative sympathetic activity predominance.[21] We did not observe a greater CAD prevalence among the overweight and obese compared to normal-weighing patients, which contrasts with that reported in previous studies.[22] Most earlier studies noted a positive association between DM and hypertension with CAD.[23,24] However, this association was not reflected in our study, which agrees with the findings of Polderman *et al*.[12] This may be due to the low prevalence of DM, hypertension, and IHD in our study. The baseline clinical characteristics of our patients, namely neurosurgical diagnosis, preoperative anxiety, and pain, were analysed for association with an abnormal ANS function. Patient anxiety levels were assessed using the NRS for anxiety in the immediate preoperative period. Preoperative pain (headache in patients with cranial abnormalities and spinal pain in patients with spine pathology) was assessed using the NRS score for pain. There was no relationship between preoperative pain or anxiety with CAD in our study cohort. Patients with chronic anxiety are known to be vulnerable to cardiovascular illnesses. However, earlier studies could not demonstrate the definitive role of ANS dysfunction as the link to this association.[25] Some of our patients did have clinically significant pain and anxiety; however, the representation was small, and this could be due to the routine anti-anxiety (tablet alprazolam 0.5 mg) and analgesic medications (tablet paracetamol 500 mg) standardly prescribed in the preoperative period to all patients in addition to patient counselling.

Our study did not show a predisposition to CAD based on neurosurgical diagnoses. This could be due to a relatively lower representation of each type of neurosurgical disease in our study. The location of neurosurgical pathology in the hypothalamus, insula, and cingulate gyrus, which regulate the ANS, can affect cardiac autonomic function.[26] However, only a few patients in our study had insular pathology, and no patient had pathology in the hypothalamus of the cingulate gyrus, which precluded separate analysis of data from these patients. Intracranial pressure (ICP) can influence autonomic function.[27] However, elective neurosurgical patients with intact consciousness were our inclusion criteria. Hence, we do not anticipate a significantly raised ICP in these patients.

There are a few limitations to our study. Firstly, we assessed CAD by using a relatively novel device, ANSiscope™. Though this instrument has been used across diverse groups of patients,[5-9] its validation with conventional ANS assessment tools is needed before routine use in the perioperative setting. Secondly, we performed the ANS function assessments in the operating room's preoperative holding area just before the induction of anaesthesia for surgery. The results of the assessments at this time may be different from more relaxed assessments done days earlier as anxiety and stress related to surgery may be maximal at the time of testing just before the surgery. Despite the high prevalence, our study's inability to identify predictors of CAD probably reflects the lack of variability in our patient population or sufficient sample size. Lastly, the heterogeneity of diagnosis in our study population precludes meaningful interpretation of the effect of neurosurgical diagnoses on HRV and ANS.

CONCLUSION

The significant prevalence of CAD observed in our study can be an important concern to patient care in the perioperative period. However, none of the proposed demographic or clinical conditions could predict CAD among our neurosurgical cohort. Knowledge about CAD status before surgery can help prepare and plan anaesthetic management better to minimise adverse cardiovascular events and improve outcomes in this high-risk population.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

Acknowledgements

Our sincere thanks to the Vision Group on Science and Technology (VGST), and the Karnataka Science and Technology Promotion Society (KSTePS), Government of Karnataka for providing financial assistance to this study.

We acknowledge our Neuro anaesthesiologist colleague Dr Shweta Naik for her valuable contribution towards the conduct of the study. We thank our Anesthesia Technicians Miss. Keerthana, Miss. Harshitha, Miss. Shilpa, Miss. Esther, Miss. Thanya, and Miss. Tejaswini for their assistance during the study data collection.

Financial support and sponsorship

This study was funded by the Vision Group on Science and Technology (VGST), under the aegis of Karnataka Science and Technology Promotion Society (KSTePS), Government of Karnataka. The sponsors had no role in the design and implementation of this clinical research.

Conflicts of interest

There are no conflicts of interest.

ORCID

Sangeetha R Palaniswamy: https://orcid.org/0000-0002-5080-5849

Dhritiman Chakrabarti: https://orcid.org/0000-0003-4804-5403

Kamath Sriganesh: https://orcid.org/0000-0003-2355-0403

Musumur Mahendranath: https://orcid.org/0000-0002-6155-2234

Sathyaprabha TN: https://orcid.org/0000-0001-9865-0586

Dwarakanath Srinivas: https://orcid.org/0000-0001-7330-0627

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