Clinical Communication

Cardiac autonomic function in post-COVID-19 patients and its impact on haemodynamics during neurosurgery – A prospective observational study

INTRODUCTION

Few patients with coronavirus disease 2019 (COVID-19) manifest new or persistent symptoms. Some post-COVID-19 manifestations are attributable to cardiac autonomic dysfunction (CAD) and occur even with mild-to-moderate COVID-19 infection.[1] CAD is assessed by heart rate variability (HRV) analysis, which is a measurement of oscillation in time intervals between consecutive heartbeats. During the acute COVID-19 phase, there is a decrease in HRV with sympathetic overactivity, followed by a compensatory phase of parasympathetic dominance.[2] After 20 weeks of COVID-19 infection, reduced parasympathetic activity is seen.[3] CAD can lead to perioperative haemodynamic instability and increased cardiovascular morbidity.[4]

Our primary objective was to compare HRV parameters between patients with and without previous COVID-19 infection. The secondary objectives were to compare intraoperative haemodynamics (heart rate [HR], systolic blood pressure [SBP], mean arterial pressure [MAP]) and postoperative outcomes between the two groups.

METHODS

This prospective observational study was conducted at a tertiary neuroscience hospital from March 2022 to February 2023 after institute ethics committee approval [(NIMHANS/31st IEC (BS and NS Div.)/2021 dated 28-08-2021)], and registration with Clinical Trials Registry-India (CTRI/2021/10/037117, www.ctri.nic.in). Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The study was carried out as per the principles of the Declaration of Helsinki, 2013. This study compared adult patients with previous COVID-19 infection (cases) and patients without COVID-19 infection (controls) for preoperative CAD, intraoperative haemodynamic instability and postoperative outcomes when they underwent elective neurosurgery under general anaesthesia. Controls were age-, gender- and diagnosis-matched patients without previous COVID-19 infection undergoing similar neurosurgeries. Patients with uncontrolled diabetes mellitus, significant cardiovascular disease, body mass index >30 kg/m^2 and those taking drugs affecting cardiac autonomic function were excluded.

Both cases and controls underwent preoperative HRV tests for evaluating CAD. HRV was recorded wirelessly from an electrocardiogram using Equivital (ADinstruments, Sydney, Australia) and analysed using LabChart Pro 8 software. The HRV parameters were analysed in the time domain: RR interval, HR (average and standard deviation [SD]), SD of RR intervals (SDRR) reflecting overall HRV, SD of successive differences (SDSD), root mean square of successive differences of RR intervals (RMSSD) and percentage of consecutive RR intervals that vary by 50 ms (pRR50) indicating parasympathetic function. The frequency domain factors analysed were total power (TP) representing total HRV, low-frequency (LF) and very-low-frequency (VLF) bands implying sympathetic activity, high-frequency (HF) band reflecting parasympathetic activity and LF/HF ratio indicating sympathetic–parasympathetic balance. Frequency parameters were reported as absolute values (ms^2) and normalised units (nu).

Standard anaesthesia induction and maintenance were performed in all patients. Intraoperative haemodynamic parameter (HR, SBP, MAP) data were obtained from the anaesthesia information management system (AIMS) (Centricity®; GE Healthcare™, Waukesha, WI). Haemodynamic instability was defined as an increase or decrease in HR, SBP and MAP by 20% and 30% of baseline. While 20% change is more commonly used, the 30% threshold provides greater insight into the extent and effect of severity of haemodynamic changes.[5] Hypotension management included 3 mg boluses of intravenous mephentermine, and if it was persistent, noradrenaline infusion was considered. For hypertension management, intravenous esmolol or labetalol was considered.

We collected data for postoperative complications of myocardial infarction, cardiac arrest, inotrope/vasopressor use or referral to cardiac centre. We collected the duration of mechanical ventilation, intensive care unit (ICU) stay, hospital stay and in-hospital mortality.

No formal sample size calculation was done for this exploratory study. Data was analysed using R-software ver. 4.1.2 (R Core Team (2023), R: A Language and Environment for Statistical Computing; R Foundation for Statistical Computing, Vienna, Austria). Data was cleaned by filtering values above and below 250 and 10 mmHg for SBP, 200 and 10 for MAP and 250 and 10 for HR. Data points excluded from the cleaning exercise were used to calculate the percentage of artefacts for each sample as a quality control measure. Samples with <10 observations were excluded. The baseline for each sample was established by taking an average of the first 10 min of data. Duration of haemodynamic instability was obtained by testing each data point of an individual sample relative to baseline with predefined 20% and 30% cut-offs and summing up each observation's duration since the previous observation. Variance for each haemodynamic variable was calculated within each sample as an averaged sum of squared deviances. Interval and ordinal scale data are represented as median and interquartile range (IQR). Group comparison was conducted using the Mann–Whitney U test for interval and ordinal scale variables and the Chi-square test for nominal variables. Correlation was performed using Pearson's product-moment correlation method. A P value of <0.05 was considered statistically significant.

RESULTS

This study included 47 patients with 24 cases (post-COVID-19). Out of 18 cranial surgeries, 11 were brain tumours, three vascular lesions, and remaining were shunt, epilepsy, colloid cyst and microvascular decompression. Among six spine surgeries, three were for lumbar spondylolisthesis, one for cervical pathology, Arnold Chiari malformation and tethered cord. The controls included 23 patients matched for age, gender and diagnosis with the cases, and they underwent similar surgeries.

There was no difference in demographic profile between the groups. The median (IQR) ages (years) of the cases and controls were 37 (30–44.25) and 40 (34–46), respectively (P = 0.456). The median duration between COVID-19 infection and surgery was 250 (59–317) days.

There was no difference in HRV parameters between the groups [Table 1]. The intraoperative haemodynamic variables are shown in Table 2. Although baseline SBP was comparable, the cumulative duration of hypertension was significantly more in cases, while hypotension was more in controls. Similarly, despite higher baseline MAP, controls had higher intraoperative hypotension and MAP variance. Baseline HR was similar between the groups, yet the duration of tachycardia was significantly longer in cases. There were no differences concerning bradycardia. Hypotension occurred mainly after anaesthesia induction and during surgical bleeding (along with tachycardia), whereas hypertension occurred during periods of stimulation (intubation, extubation, surgical stimuli). In the control group, 15 patients (88.2%) developed severe (>30% decrease) hypotension of a minimum of 5 min, whereas 10 patients (47.6%) developed severe hypotension among cases.

There were no postoperative complications in both the groups. Two cases, but no controls, required ICU admission. There was no difference in duration of hospital stay (4 [3.5–5.5] vs. 4.5 [3.75–6.25] days), ICU stay or mechanical ventilation between the groups.

The LF/HF ratio (r = 0.42, P = 0.04) and LF (nu) (r = 0.41, P = 0.045) had a positive correlation with duration since COVID-19 infection, while HF (nu) (r = –0.47, P = 0.021) had a negative correlation with time [Table 3].

DISCUSSION

This study did not observe differences in HRV parameters between patients with and without previous COVID-19 infection. The stress of anaesthesia and surgery unmasked sympathetic imbalance, resulting in intraoperative hypertension and tachycardia in post-COVID-19 patients.

The incidence of CAD is 15% one month after COVID-19 infection.[6] In the acute phase, COVID-19 patients receiving mechanical ventilation have reduced HRV and sympathetic hyperactivity with low vagal activity.[7] After 3 months, the parasympathetic component overtakes, with increased HRV (SD of normal RR interval [SDNN] and RMSSD).[1] However, the increased parasympathetic tone is also observed during the acute phase.[8] The lower values of HRV indices (RR interval, SDNN, and RMSSD) predict myocardial injury after COVID-19.[9] We did not observe differences in HRV parameters between patients with and without previous COVID-19 infection. One reason could be a longer duration between HRV assessment

Table 1: Comparison of preoperative HRV parameters between the two groups

Parameters	Control group (*n*=23)	Post-COVID-19 group (*n*=24)	Estimate (95% CL)	*P*
Median RR interval (ms)	757.76 (626.91–880.83)	749.98 (588.87–880.86)	35.1 (−78.13, 128.86)	0.489
SDRR	26.62 (21.57–48.66)	31.35 (25.01–45.43)	-3.48 (-11.47, 6.39)	0.506
CVRR (ms)	0.04 (0.03–0.06)	0.04 (0.03–0.06)	0 (-0.02, 0.01)	0.562
Average HR (beats/min)	79.19 (68.8–96.16)	80.34 (68.48–101.87)	-3.73 (-15.58, 8.14)	0.493
SD rate	3.24 (2.62–4.62)	3.43 (2.82–5.27)	-0.29 (-1.26, 0.51)	0.548
SDSD	24.57 (16.04–29.17)	28.13 (16.08–54.72)	−7.84 (-21.65, 2.61)	0.140
RMSSD (ms)	24.55 (16.02–29.13)	28.11 (16.08–54.69)	−7.84 (-21.63, 2.59)	0.140
pRR50	4.9 (0.63–8.94)	4.54 (0.14–27.37)	-0.27 (−7.87, 2.02)	0.692
Total power	690.49 (527.39–2426.84)	1194.43 (558.86–2359.28)	-123.15 (−853.56, 474.93)	0.712
VLF power	371.1 (164.92–819.29)	437.7 (274.45–670.37)	−40.83 (-268.27, 190.36)	0.666
VLF (percentage)	41.96 (32.93–54.72)	42.66 (28.33–54.59)	0.93 (-10.12, 12.01)	0.874
LF power	227.56 (100.01–792.55)	279.96 (99.78–540.39)	20.69 (-150.77, 210.04)	0.825
LF (percentage)	24.07 (18.06–35.34)	25.07 (17.63–29.36)	2.82 (−4.71, 10.51)	0.520
LF (nu)	52.19 (35.04–70.73)	42.94 (30.74–61.6)	7.29 (−7.19, 21.23)	0.392
HF power	242.86 (77–520.73)	315.6 (59.46–1068.35)	−50.44 (−424.58, 98.9)	0.520
HF (percentage)	21.71 (16.41–37.27)	32.93 (14.64–41.32)	−5.23 (-15.72, 5.91)	0.479
HF (nu)	39.19 (28.56–62.85)	51.83 (34–65.78)	−7.43 (-19.58, 5.97)	0.381
LF/HF ratio	1.17 (0.56–2.49)	0.84 (0.49–1.72)	0.3 (-0.25, 0.99)	0.358

Data are expressed as median (interquartile range). Estimate is median of the difference between groups. CL=confidence levels, CVRR=coefficient of variation of R–R interval, HF=high frequency, HRV=heart rate variability, LF=low frequency, nu=normalised units, pRR50=percentage of successive R–R intervals that differ by more than 50 ms, RMSSD=root mean square of successive differences, SDRR=standard deviation of R–R intervals, SDSD=SD of successive differences, VLF=very low frequency

Table 2: Comparison of intraoperative haemodynamic complications between the groups

Parameters	Control group (*n*=23)	Post-COVID-19 group (*n*=24)	Estimate (95% CL)	*P*
Baseline SBP (mmHg)	128.33 (123–150)	125 (105–131.25)	13.58 (-1.3, 30)	0.097
SBP variance	236.22 (133.46–365.4)	175.47 (135.88–259.01)	44.66 (-29.73, 154.03)	0.281
Duration of hypertension (SBP >20% of baseline) in seconds	0 (0–900)	480 (120–2100)	-180 (-1748, 0)	0.042
Duration of hypertension (SBP >30% of baseline) in seconds	0 (0–60)	180 (0–480)	-120 (-300, 0)	0.043
Duration of hypotension (SBP <20% of baseline) in seconds	6540 (4200–11700)	1020 (180–6001)	5279 (1256, 8100)	0.008
Duration of hypotension (SBP <30% of baseline) in seconds	1680 (300–5047)	60 (0–360)	1380 (120, 3123)	0.005
Baseline MAP	101.88 (93.38–120)	91 (81–100.13)	12.33 (1, 23.17)	0.034
MAP variance	155.45 (128.88–294)	105.28 (81.44–162.67)	52.42 (1.04, 103.08)	0.045
Duration of hypertension (MAP >20% of baseline) in seconds	0 (0–660)	300 (60–1022)	−60 (−539, 0)	0.128
Duration of hypertension (MAP >30% of baseline) in seconds	0 (0–360)	60 (0–300)	0 (-120, 0)	0.400
Duration of hypotension (MAP <20% of baseline) in seconds	8220 (6601–11700)	3420 (540–9061)	4920 (900, 7861)	0.017
Duration of hypotension (MAP <30% of baseline) in seconds	2762 (960–5003)	121 (60–1020)	1501 (541, 4266)	0.011
Baseline HR (beats/min)	86.7 (70.9–95.81)	77.88 (68.25–93.88)	3 (-10.45, 16.75)	0.691
HR variance	89.64 (79.06–161.22)	125.37 (78.11–184.74)	-19.14 (−76.98, 26.95)	0.486
Duration of tachycardia (>20% of baseline) in seconds	240 (105–853.75)	1530 (345–9482.5)	−970.35 (−7980, -121)	0.006
Duration of tachycardia (>30% of baseline) in seconds	120 (0–300)	540 (285–3155.5)	-360.73 (-1980, -120)	0.004
Duration of bradycardia (<20% of baseline) in seconds	4110 (165–9555)	60 (0–4455.75)	1503.56 (0, 7380)	0.051
Duration of bradycardia (<30%) in seconds	30 (0–5069.75)	0 (0–134.75)	0 (0, 4740)	0.160

Values are described as median (interquartile range). Estimate is median of the difference between groups. CL=confidence levels, COVID-19=coronavirus disease 2019, HR=heart rate, MAP=mean arterial pressure, SBP=systolic blood pressure

and COVID-19 infection, as noted in an earlier study.[10] Another reason could be the non-severe nature of previous COVID-19 infections.

Despite no difference in preoperative HRV parameters, we observed significant differences in intraoperative haemodynamic complications between patients with and without previous COVID-19 infection. Cases manifested with intraoperative hypertension, while controls developed hypotension with higher variance in MAP. Duration of tachycardia was longer in cases than in controls, while bradycardia was similar. These findings suggest the manifestation of sympathetic hyperactivity in patients with previous COVID-19 infection consequent to the stress of surgery and anaesthesia. Compared to non-infected individuals, sympathetic excitation with a reduction in parasympathetic modulation is reported in long-COVID-19 patients.[11] We noted a positive correlation between the LF/HF ratio and LF

Table 3: Correlation of HRV parameters with duration from COVID-19 infection

Variable	Coefficient (95% CL)	*P*
Median RR interval (in ms)	-0.32 (-0.64, 0.1)	0.129
SDRR	-0.38 (-0.68, 0.02)	0.065
CVRR (in ms)	-0.26 (-0.6, 0.16)	0.226
Median heart rate (beats/min)	0.41 (0.01, 0.7)	0.047
SD rate	-0.23 (-0.58, 0.19)	0.287
SDSD	-0.31 (-0.63, 0.11)	0.147
RMSSD (ms)	-0.31 (-0.63, 0.11)	0.146
pRR50	-0.35 (-0.66, 0.06)	0.095
Total power	-0.25 (-0.6, 0.17)	0.230
VLF power	-0.21 (-0.56, 0.22)	0.334
VLF (percentage)	0.15 (-0.27, 0.53)	0.470
LF power	-0.26 (-0.6, 0.16)	0.217
LF (percentage)	0.26 (-0.16, 0.6)	0.227
LF (nu)	0.41 (0.01, 0.7)	0.045
HF power	-0.27 (-0.61, 0.15)	0.206
HF (percentage)	-0.36 (-0.67, 0.05)	0.084
HF (nu)	-0.47 (-0.73, -0.08)	0.021
LF/HF ratio	0.42 (0.02, 0.71)	0.040

CL=confidence limits, COVID-19=coronavirus disease 2019, CVRR=coefficient of variation of R–R interval, HF=high frequency, HRV=heart rate variability, LF=low frequency, nu=normalised units, pRR50=percentage of successive R–R intervals that differ by more than 50 ms, RMSSD=root mean square of successive differences, SD=standard deviation, SDRR=standard deviation of R–R intervals, SDSD=SD of successive differences, VLF=very low frequency

and a negative correlation between HF and duration since COVID-19 infection. This suggests sympathetic dominance and decreasing parasympathetic activity with time after the COVID-19 infection.

In our study, although tachycardia and hypertension did not adversely affect perioperative outcomes in cases, it may happen in vulnerable patients with pre-existing cardiovascular comorbidities. Moreover, mortality is high in neurosurgical patients with COVID-19 infection.[12] The anaesthesiologist should anticipate and prepare for perioperative haemodynamic upswings in post-COVID-19 patients, which will help reduce complications and improve the outcomes.

The limitations of our study are the small sample size, impedement in generalisability of our findings to non-neurosurgical procedures, and heterogeneous neurosurgical diagnoses.

CONCLUSION

The preoperative cardiac autonomic function was normal and similar in neurosurgical patients with and without previous COVID-19 infection. Patients with previous COVID-19 infection manifested with tachycardia and hypertension during stressful periods of anaesthesia and surgery. Postoperative outcomes were, however, similar in both groups. Hence, no definitive conclusions regarding the impact of post-COVID-19 status on CAD and consequent perioperative complications can be drawn from this study.

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.

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Conflicts of interest

There are no conflicts of interest.

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