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Original Article

Evaluation of Cardiac Function in Patients with Supratentorial Tumors and Raised Intracranial Pressure: HABIT-ICP, a Prospective Observational Study Using Transthoracic Echocardiography

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Abstract

Objectives An acute increase in intracranial pressure (ICP) has been shown to affect cardiac function due to brain ischemia and the associated increased sympathetic activity. However, there is limited literature on the changes in cardiac function in clinical scenarios where there is a gradual and progressive increase in ICP, such as in brain tumors. We aimed to assess and compare the cardiac function in patients with primary supratentorial brain tumors presenting with and without raised ICP for neurosurgery.

Materials and Methods In this prospective observational study, we included 60 patients; Group I (30 patients without features of raised ICP) and Group II (30 patients with features of raised ICP). Transthoracic echocardiography was performed on the day before the surgery and the seventh postoperative day. Hemodynamic, electrocardiographic, and echocardiographic parameters were obtained during pre-, intra-, and postoperative periods and were used for statistical analysis.

Results We found an increased relative wall thickness and an increased incidence of systolic (22%) and diastolic dysfunction (33.3%) in Group II compared with Group I patients. There was an increased incidence of intraoperative adverse events such as postinduction hypotension and vasopressor use in Group II patients. In the postoperative period, there was an improvement in the systolic function; however, the chamber dimensions and diastolic dysfunction did not improve significantly.

Conclusion Our study suggests that raised ICP might contribute to the pathophysiology of sympathetic overactivity and sympathetically driven cardiac dysfunction, which does not entirely revert in the immediate postoperative period.

Keywords
- echocardiography
- intracranial pressure
- neurosurgery
- perioperative
- implications
- supratentorial brain tumor

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Introduction

Brain injury or alterations in the cerebral physiology can result in multiorgan dysfunction. This is due to the influence of the brain on the control of various body organ systems. The effects of the injured brain on alterations in the cardiovascular system represent an example of organ cross-talk wherein the nervous system causes pathological influences on various body systems.[1–4] The impact of the resultant cardiac dysfunction can cause deleterious secondary insult to the brain, which could adversely affect the prognosis of neurosurgical patients.

The research on heart–brain interactions in the setting of pathological conditions producing an acute rise in intracranial pressure (ICP) such as in stroke and traumatic brain injury (TBI) is overwhelming; however, there is a lacuna of literature in the setting of chronically raised ICP in the brain tumors. It is pertinent to understand the brain–heart interactions in such conditions since cardiac dysfunction could potentially impact the prognosis of these patients.

We conducted this prospective observational study: *H*eart *A*nd *B*rain *I*nteractions in *T*umors with raised *ICP* (HABIT-ICP), to assess the impact of raised ICP on cardiac function, in patients with primary supratentorial tumors presenting for resection.

We hypothesized that in these patients with features of raised ICP, there will be an impairment of cardiac function which will be reversed once ICP is normalized after the neurosurgical procedure.

Materials and Methods

This prospective observational study was approved by the Institutional Ethics Committee (SCT/IEC/2018/1242) prior to the enrollment of the first subject. Written informed consent was obtained from all participating subjects or their legal representative. Inclusion criteria were as follows: American Society of Anesthesiologists 1 and 2 patients aged between 18 and 60 years presenting with supratentorial tumors. Exclusion criteria were as follows: diabetes mellitus, hypertension, vascular diseases, chronic obstructive pulmonary disease, known cardiac illness, poor echo window, obesity, prior history of chemotherapy or radiotherapy, pregnant or lactating mothers, lesions in the prefrontal cortex, insula, hypothalamus, amygdala and, hippocampus. The subjects were classified into two groups: Group I consisted of 30 patients without clinical and/or radiological features of raised ICP, and Group II consisted of 30 adult patients with clinical and radiological features of raised ICP (persistent headache, visual disturbances, vomiting, papilledema, computed tomography [CT]/magnetic resonance imaging [MRI] scan showing cerebral edema, midline shift > 5 mm, hydrocephalus, CT optic nerve sheath diameter [CT-ONSD > 5.6 mm]).

Anesthesia protocol was standardized for all the patients included in the study. The following parameters were recorded 24 hours prior to the surgery: demographic data, primary diagnosis and the proposed procedure, Glasgow coma scale, heart rate (HR), blood pressure (BP), presence or absence of features of raised ICP (clinical signs and symptoms, fundus examination, CT/MRI findings of raised ICP), CT-ONSD value, medication history, and electrocardiography (ECG) changes. In all the recruited patients, cardiac function was evaluated with transthoracic echocardiography (TTE) using a 2-MHz (S2–4) phased array probe (Vivid I GE Health Care, Milwaukee, United States). TTE was done using standard views as per the recommendations of the British Society of Echocardiography. The echocardiographic variables were classified as chamber dimensions, left ventricular (LV) systolic function, LV diastolic function, and right ventricular systolic function. The TTE was performed twice in the study period; the first one 24 hours prior to the scheduled neurosurgical procedure, (T0) and the other on the seventh postoperative day following the tumor removal (T1). During the intraoperative period, any use of vasoactive drugs in the postinduction period, intraoperative hemodynamic parameters, and amount of blood loss were recorded.

Statistical Analysis

The statistical analyses were done using SPSS software version 21.0 (Chicago, SPSS Inc.) We performed the following two analyses of the recorded data: Intergroup analysis to evaluate whether the variables about cardiac function were different between the two groups. Intragroup analysis to evaluate whether the variables were different before and after neurosurgery.

The normality of the distribution was tested by the Shapiro–Wilk's test. Observations obtained from the study were expressed in mean ± standard deviation. Comparison of categorical variables was done using the chi-square test. Comparison of normally distributed continuous variables was evaluated with the Student's *t*-test. A *p*-value of less than 0. 05 was considered statistically significant.

Results

A total of 84 patients were enrolled in the study. Eight patients in Group I and 16 patients in Group II had postoperative complications and were excluded (►**Fig. 1**).

There was no significant difference ($p > 0.05$) between the two groups in terms of demographic data (►**Table 1**). The baseline HR was within the normal range and was not different between the two groups. Patients in Group II had a significantly higher systolic BP (128 ± 14.3 vs. 115.3 ± 10.9 mm Hg, $p < 0.05$) and diastolic BP (78.9 ± 7.9 vs. 73.5 ± 6.5 mm Hg, $p < 0.05$) when compared with Group I. Ten patients (30%) in Group II had ECG changes of which 14.8% of patients had ST depression, 11% had T inversion, and 11% had sinus bradycardia as compared with one person in Group I who had ST depression. Group II patients had a significantly higher incidence of postinduction hypotension (66.6%), increased vasopressor use (73.3%), and higher intraoperative blood transfusion (66.6%) as compared with Group I.

Cardiac Function

Chamber Dimensions

Baseline LV dimensions in systole (left ventricular internal diameter end-systole [LVIDs]) were lesser in Group II

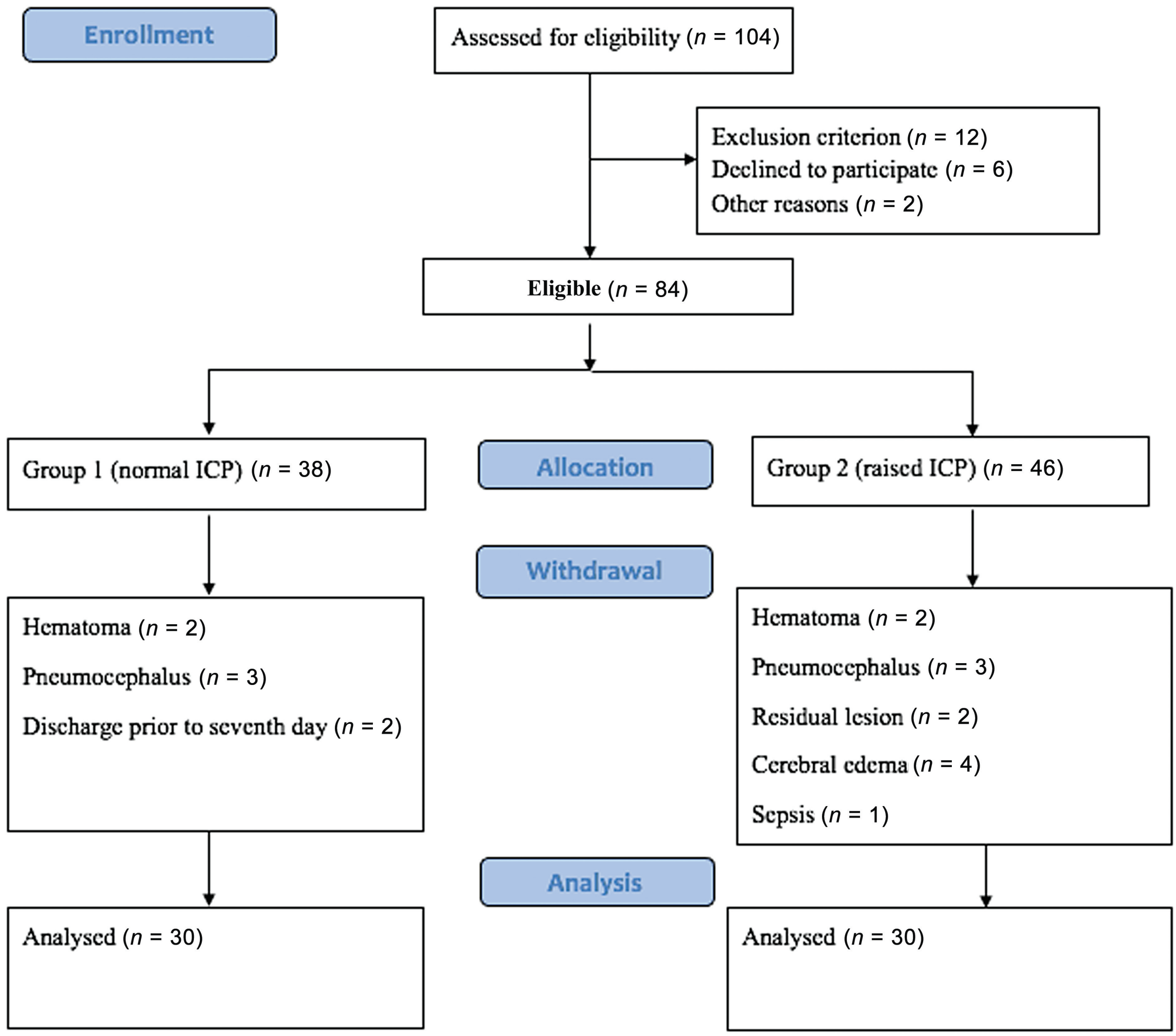

Fig. 1 The Consolidated Standards of Reporting Trials flow diagram.

Table 1 Comparison of basic demographic data in the two groups

Variables	Group I ($n = 30$)	Group II ($n = 30$)	p-Value
	Mean ± SD	Mean ± SD	
Age (y)	35.5 ± 9.6	38.5 ± 9.8	0.241
Weight (kg)	65.7 ± 9.3	62.5 ± 10.0	0.214
Height (cm)	164.3 ± 6.9	162.2 ± 9.8	0.349
Body surface area (m^2)	1.7 ± 0.1	1.7 ± 0.2	0.211
Body mass index (kg/m^2)	24.3 ± 2.9	23.7 ± 2.9	0.433

Abbreviation: SD, standard deviation.

compared with Group I. Compared with Group I, the inferior wall dimensions were greater in both diastole and systole in Group II. During the preoperative period, the relative wall thickness (RWT) in Group II was also higher than that of Group I (►**Table 2**). The chamber dimensions did not differ between the preoperative and postoperative periods in both groups.

Ventricular Functions

During the preoperative period, eight patients (26.7%) in Group II had systolic dysfunction of whom seven patients (23.3%) had mild LV dysfunction and one patient (3.3%) had moderate LV dysfunction. In Group II patients, the ejection fraction (EF) in the postoperative period showed an increased value (68.48 ± 9.63%) compared with preoperative values

Table 2 Comparison of the cardiac chamber dimensions in the two groups in the pre- and postoperative periods

Chamber dimensions		Group I ($n=30$)	Group II ($n=30$)	*p*-Value
		Mean ± SD	Mean ± SD	
LVIDd (cm)	Preoperative	4.22 ± 0.43	3.98 ± 0.93	0.218
	Postoperative	4.19 ± 0.26	3.92 ± 0.91	0.128
LVIDs (cm)	Preoperative	2.89 ± 0.36	2.52 ± 0.81	**0.025**
	Postoperative	2.90 ± 0.34	2.47 ± 0.85	**0.013**
IWIDd (cm)	Preoperative	0.92 ± 0.20	1.09 ± 0.36	**0.025**
	Postoperative	0.92 ± 0.19	1.12 ± 0.45	**0.032**
IWIDs (cm)	Preoperative	1.06 ± 0.28	1.42 ± 0.34	**0.000**
	Postoperative	1.17 ± 0.35	1.41 ± 0.51	**0.040**
IVSd (cm)	Preoperative	1.01 ± 0.20	1.01 ± 0.37	0.971
	Postoperative	1.05 ± 0.28	0.97 ± 0.28	0.326
IVSs (cm)	Preoperative	1.10 ± 0.25	1.26 ± 0.45	0.107
	Postoperative	1.14 ± 0.35	1.19 ± 0.36	0.657
RWT	Preoperative	0.44 ± 0.14	0.63 ± 0.43	**0.028**
	Postoperative	0.44 ± 0.08	0.62 ± 0.35	**0.008**
LVMI (g/m^2)	Preoperative	77.4 ± 19.9	82.5 ± 30.5	0.456
	Postoperative	79.3 ± 25.6	82.9 ± 41.2	0.688

Note: The *p*-Value < 0.05 is statistically significant.
Abbreviations: IVSd, interventricular septum thickness end-diastole; IVSs, interventricular septum thickness systole; IWIDd, inferior wall internal diameter end-diastole; IWIDs, inferior wall internal diameter end-systole; LVIDd, left ventricular internal diameter end-diastole; LVIDs, left ventricular internal diameter end-systole; LVMI, left ventricular mass index; RWT, relative wall thickness; SD, standard deviation.

(61 ± 12.25%) ($p < 0.001$) (►**Fig. 2**). In the postoperative period, none of the patients had LV systolic dysfunction. In both the groups, right ventricular systolic function using tricuspid annular plane systolic excursion did not differ between the groups in both the pre- and postoperative periods.

None of the patients in Group I had diastolic dysfunction before and after neurosurgery. However, in Group II, 33.3% of patients had diastolic dysfunction during the preoperative period and 30% of patients had diastolic dysfunction in the postoperative period ($p < 0.9$) (►**Fig. 3**). Moreover, the indices of LV filling pressure such as E/E′ and left atrial (LA) volume were significantly higher in Group II compared with Group I (►**Table 3**).

Discussion

Even though heart–brain cross-talk has garnered much attention and raised ICP has been implicated as a cause for neurocardiac syndromes, there is a dearth of scientific data which address the cardiac effects of the subacute and chronic rise in ICP which is encountered in patients with supratentorial tumors.

We evaluated the cardiac function of these patients and the reversibility of the cardiac dysfunction (if present in the preoperative period) after surgical decompression.

Hemodynamic Variables

In our study, the BP of patients with raised ICP was significantly higher than that of patients with normal ICP. Cushing's response, which is an agonal and terminal event, consists of the triad of hypertension, bradycardia, and apnea. It is traditionally thought to be produced by brain stem ischemia leading to a sympathetic activation response. However, it is debated that this reflex could be a part of a physiological reflex mechanism for BP regulation even in scenarios with minimally increased ICP. This debate was further strengthened by various animal studies which has demonstrated that changes in BP were parallel to small changes in ICP.[5–10] Schmidt et al demonstrated a high incidence of hypertension and HR variance in awake patients having a modest and gradual rise in ICP.[10] Schmidt et al demonstrated that a modest 7 mm Hg ICP rise from 8 to 15 mm Hg significantly increased sympathetic activity by 17%. Both in mice and humans, a modest increase in ICP augmented the muscle sympathetic nerve activity (MSNA) which is a quantitative measurement of sympathetic tone. Furthermore, the decrease in ICP was associated with a significant reduction in MSNA, thereby proving the reversibility of the sympathetic activation once the ICP is normalized.[11] Hence, animal and clinical studies suggest that even a minimal increase in ICP change can modulate systemic hemodynamics probably via the sympathetic nervous system (SNS) and result in hypertension.

The differences in BP between the two groups in our study signposts toward similar pathophysiology, wherein the patients with raised ICP had increased BP due to an increased sympathetic activity.

Electrocardiographic Changes

Patients with raised ICP showed ECG changes in the form of repolarization abnormalities and bradycardia. ECG changes

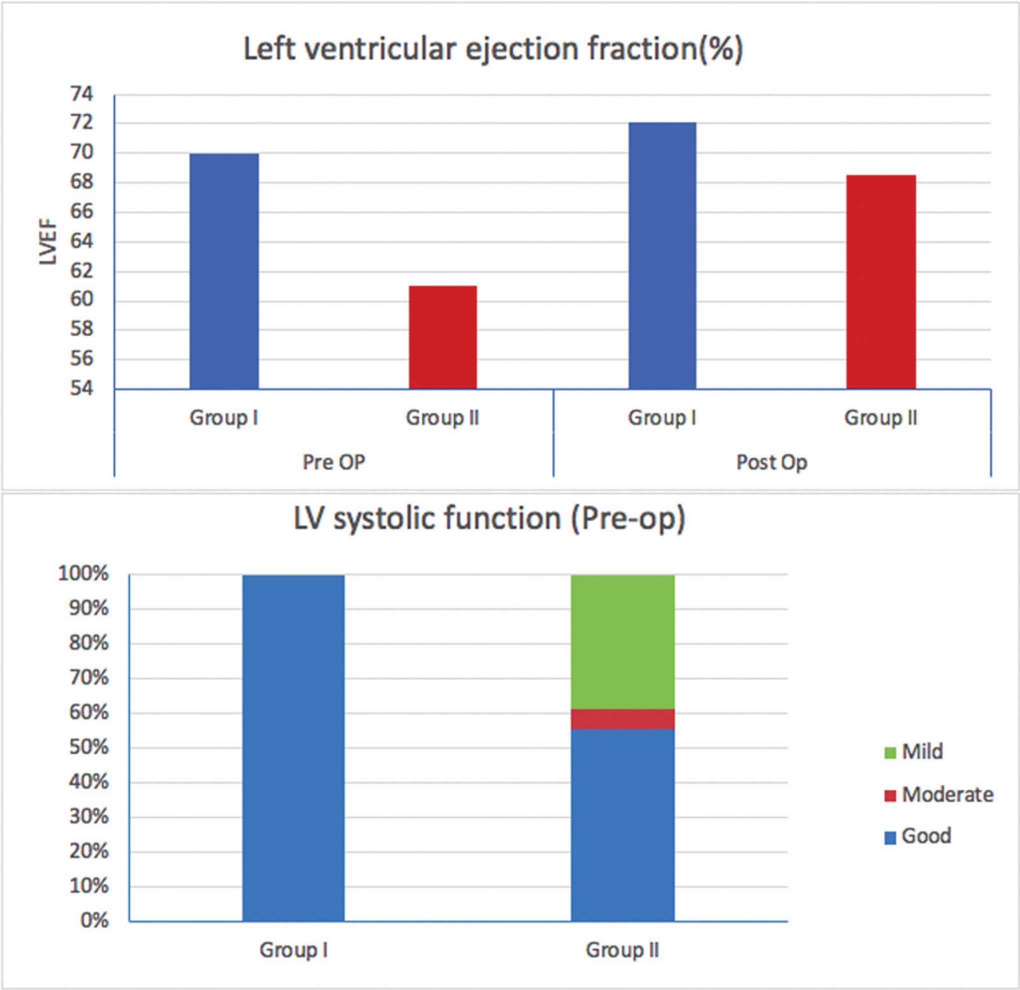

Fig. 2 Bar graph showing the ejection fraction and systolic function of both the groups in the pre- and postoperative periods. LVEF, left ventricular ejection fraction.

in acute brain injury such as TBI, subarachnoid hemorrhage (SAH), and stroke have been described in the literature wherein common manifestations included arrhythmias and repolarization abnormalities. Koepp et al have found that 40% of patients with brain tumors had ECG changes, especially QTc prolongation. They also noted that tumors involving the limbic system had a higher percentage of ECG abnormalities compared with the extra limbic system; however, their study excluded patients with raised ICP.[12] We also noted that the ECG changes indicate abnormalities of repolarization and subendocardial ischemia. The plausible reason could be the activation of the SNS resulting in subclinical effects on the myocardium.

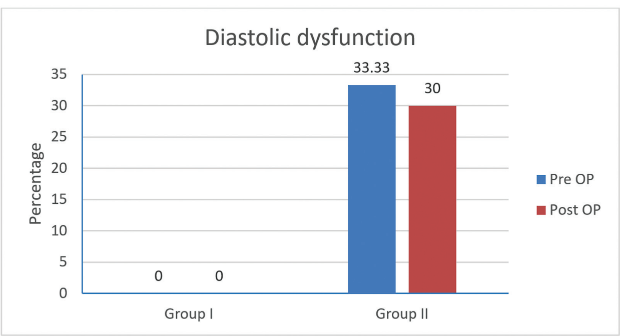

Fig. 3 Bar graph showing comparison of diastolic dysfunction between the two groups during pre- and postoperative periods.

Echocardiographic Evaluation

Chamber Dimensions

In the raised ICP group, an increased RWT was accompanied by a normal LV mass index (LVMI), which denotes a concentric remodeling pattern. Our study results of increased wall thickness and decreased LV chamber dimensions are consistent with the study by Ferrera et al, who evaluated the acute changes in the myocardial function of Wistar rats with raised ICP.[13] They concluded that the raised ICP is associated with the autonomic storm causing interstitial myocardial edema leading to myocardial wall hypertrophy.

It is found that there is a significant positive correlation between sympathetic activity and LVMI.[14] Central sympathetic activation is associated with the development of LV hypertrophy in human hypertension. The presence of concentric remodeling and hypertension seen in our study of patients with raised ICP could be most likely due to chronic sympathetic

Table 3 Comparison of the parameters relevant to left ventricular diastolic function in the two groups

Variables		Group I ($n = 30$)	Group II ($n = 30$)	*p*-Value
		Mean ± SD	Mean ± SD	
E vel (m/s)	Preoperative	0.81 ± 0.07	0.73 ± 0.22	0.061
	Postoperative	0.81 ± 0.08	0.78 ± 0.17	0.371
E/A	Preoperative	1.51 ± 0.26	1.49 ± 0.68	0.870
	Postoperative	1.44 ± 0.17	1.48 ± 0.49	0.664
e′ (m/s)	Preoperative	0.12 ± 0.02	0.10 ± 0.03	**0.001**
	Postoperative	0.23 ± 0.36	0.11 ± 0.03	0.09
E/e′	Preoperative	6.87 ± 1.32	8.26 ± 3.25	**0.036**
	Postoperative	5.99 ± 1.91	7.94 ± 2.52	**0.002**
Dec T (ms)	Preoperative	214.2 ± 36.9	196.8 ± 81.7	0.297
	Postoperative	225.6 ± 44.1	229.6 ± 65.8	0.791
LA vol index (mL/m^2)	Preoperative	21.6 ± 2.3	24.3 ± 2.6	**0.000**
	Postoperative	21.8 ± 2.5	24.6 ± 2.4	**0.000**

Abbreviations: Dec T, deceleration time; E vel, peak early mitral valve velocity; e′, early diastolic velocity; LA vol index, left atrial volume index; SD, standard deviation.

activation. Moreover, in our study, Group II patients had reduced LVIDs with increased FS, indicative of increased cardiac workload due to sympathetic stimulation.[15] This hypercontractile state observed in the raised ICP group further strengthens the postulation of chronic sympathetic hyperactivity activity prevalent in this subgroup.

Systolic Function

In the setting of neurological injury, sympathetic overactivity and higher levels of circulating endogenous catecholamines have been implicated in the pathogenesis of LV dysfunction. This could explain the systolic dysfunction found in the patients with raised ICP.

Krishnamoorthy et al, in their study of adult TBI patients, assessed systolic function and found that 22% of their patients had systolic dysfunction, and all patients with early systolic function recovered after 1 week.[16] Animal studies have shown that chronic sympathetic stimulation can lead to increased wall thickness as early as 1 month and LV systolic pump dysfunction at 6 months without intrinsic myocardial failure.[17] Increased sympathetic activity has also been found to be associated with a reduction in EF and chronic systolic dysfunction.[18] Our study also shows similar findings in patients with raised ICP, whereas in those without feature of increased ICP, there were no changes in LV structure and LV systolic function.

Diastolic Function

The diastolic dysfunction in the patients with raised ICP could be attributed to the increased wall thickness and concentric remodeling contributing to reduced LV compliance as evidenced by a higher LA volume index in Group II patients. The LV diastolic dysfunction in the raised ICP population could be due to the effects of chronic sympathetic activity and myocardial norepinephrine discharge encountered in this subset. This subsequently increases the cytosolic calcium in cardiac muscle cells, causing an impediment to myocardial relaxation and resulting in diastolic dysfunction. This is supported by the study done by de Souza et al, who found that the presence of asymptomatic LV diastolic dysfunction is associated with increased MSNA, independent of BP control.[19]

Diastolic dysfunction has been found in other acute neurological diseases such as TBI and SAH. Kopelnik et al in their study demonstrated a higher incidence of late-onset diastolic dysfunction in contrast to the peaking of troponins in the initial days' post-SAH.[20] They suggested that this might be because that diastolic dysfunction is seen in a persistent form of neurocardiac damage.

Ferrera et al evaluated echocardiographic and histological changes in the heart during brain death.[13] They postulated that intracranial hypertension induces an autonomic storm that could result in myocardial injury by causing intracellular calcium overload, free radicals production, and interstitial myocardial edema. This can lead to fibrosis resulting in progressive stiffness of the LV leading to diastolic stiffness, impaired relaxation, and diastolic dysfunction.

Reversibility of Cardiac Dysfunction

It is noteworthy that in our study, we observed that the systolic dysfunction reverted postsurgery, whereas the chamber dimensions and diastolic dysfunction persisted. The reason for this partial reversal of cardiac function is a question to ponder. It could be that stimulus for sympathetic overactivity was abolished postnormalization of ICP, thus leading to an improvement in the systolic function. Since the wall thickness did not normalize after the surgery, the concentric remodeling and decreased LV compliance could have persisted in the postoperative period. The resultant increase in the afterload and LV diastolic dysfunction could take a longer time to resolve.

Clinical Implications

LV dysfunction is associated with an increased incidence of perioperative complications.[21] In our study population, patients with primary brain tumors with raised ICP had an increased incidence of LV dysfunction and postinduction hypotension. This could be deleterious as the cerebral perfusion pressure is already compromised in this subgroup, and any further drop in BP could result in severe neurological injury.

Diastolic dysfunction is an independent predictor of postoperative pulmonary edema and major cardiac events in patients undergoing low- and intermediate-risk surgery. Moreover, it is independently associated with postoperative adverse events and increased hospital length of stay.[21] Patients with initial stages of diastolic dysfunction are usually asymptomatic at rest, but neurosurgery and anesthesia are scenarios that stress the cardiovascular system beyond its physiological reserve. The effects of induction drugs on cardiac inotropy and lusitropy as well as vasodilation caused by them can also contribute to hypotension requiring vasopressors.

Limitations

This study was done in patients of a single institute; a larger multicenter trial may be required to confirm our findings. We have analyzed the postoperative echocardiogram only on the seventh postoperative day. Though stunned neurogenic myocardium is transient and reversible mostly after a week, this may not be similar to the pathophysiology or changes encountered in the tumor population of our study. Whether the cardiac dysfunction in patients with raised ICP is reversible after a few weeks or months should be a question for further studies.

We did not quantitatively measure the ICP or markers of cardiac dysfunction such as troponin in this study. Future studies evaluating the same are required for correlation with the severity of cardiac dysfunction and prognostication.

Conclusion

In conclusion, we demonstrated that in patients with supratentorial brain tumors and raised ICP, there was significant elevation of BP, ECG changes, changes in cardiac structure, and features of LV systolic and diastolic dysfunction. Though systolic function improved in the postoperative period, changes in LV chamber dimensions and diastolic dysfunction did not revert. These changes could be expounded by increased sympathetic activity in response to rising ICP and impaired cerebral perfusion. Future studies with a larger population are required to understand the pathogenesis, implications of cardiac abnormalities, as well as the long-term reversibility of the cardiac functions, in this subset of patients.

Note

The abstract was presented for the Neuroanaesthesia and Critical Care Society Annual Conference on May 12, 2023, at Nottingham, United Kingdom, and was shortlisted for the Harvey Granat Prize.

Authors' Contributions

M.S., A.P.H, N.A, U.P., S.V., and R.P.C.S. approved the final manuscript. All authors contributed to the conception and design of the study, analysis and acquisition of data, interpretation of the results, and were actively involved in drafting the article and revising it critically for important intellectual content.

Ethical Approval

This prospective observational study was approved by the Institutional Ethics Committee (SCT/IEC/2018/1242) prior to the enrollment of the first subject. Written informed consent was obtained from all participating subjects or their legal representative.

Funding

None.

Conflict of Interest

None declared.

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