neurocritical care society Neurocrit Care (2008) 8:366–373
DOI 10.1007/s12028-008-9067-x

ORIGINAL PAPER

Hypothalamic Injury as a Cause of Refractory Hypotension after Sellar Region Tumor Surgery

K. A. Popugaev · I. A. Savin · A. S. Goriachev · B. A. Kadashev

Published online: 25 March 2008

Abstract
Introduction Fluid-resistant arterial hypotension can result in hypoperfusion of the brain and other organs. Well-known causes of arterial hypotension in neurosurgical practice include cardiac failure, septic shock, adrenal insufficiency, brainstem, and cervical spinal cord damage. Fluid-resistant arterial hypotension can occur in patients with brain edema without damage to brainstem when hypothalamic nuclei suffer. This phenomenon is not a well-documented cause of hypotension.
Methods We prospectively investigated 15 cases with clinical syndrome of arterial hypotension in patients following surgery for sellar region tumors. These cases were taken from 1005 patients operated between May 2003 and December 2005. Pulmonary artery catheter was used to investigate hemodynamic profile.
Results The mechanism of arterial hypotension consisted of decrease of vascular tone (SVRI was 1503 ± 624 dyn·s·cm^5·m^2) and relative hypovolemia (CVP: 4.5 ± 2.6 torr, PAWP: 7.4 ± 3.5 torr). In all cases arterial hypotension was corrected with phenylephrine after failure to respond to fluid resuscitation alone. Fluid balance was positive over the next 72 h. Twenty-seven percent of patients had transitory thyroid insufficiency. In these situations dopamine was administrated as symptomatic therapy and dose of thyroid hormone was increased. Mortality was 53%.
Conclusion Hypothalamic damage can result in life-threatening vasodilatory arterial hypotension after sellar region tumor surgery. β-Sympatomimetics are indicated in cases with thyroid insufficiency.

Keywords Arterial hypotension · α-Sympatomimetics · Phenylephrine · β-Sympatomimetics · Sellar region tumor · Hypothalamus damage · Thyroid insufficiency

K. A. Popugaev (✉) · I. A. Savin · A. S. Goriachev
Neurocritical Care Department, N.N. Burdenko Neurosurgical Research Institute, Russian Academy of Medical Sciences, Moscow, Russian Federation
e-mail: kpopugaev@nsi.ru

B. A. Kadashev
Neurosurgical Department, N.N. Burdenko Neurosurgical Research Institute, Russian Academy of Medical Sciences, Moscow, Russian Federation

Introduction

Fluid-resistant arterial hypotension can result in hypoperfusion of the brain and other organs. For patients with traumatic brain injury (TBI), short-term episodes of arterial hypotension worsen outcomes [1, 2]. Well-known causes of arterial hypotension in the neurosurgical ICU are cardiac failure, septic shock, and adrenal insufficiency [3]. Moreover, in neurosurgical practice, arterial hypotension can develop in cases with brain stem and cervical/upper thoracic spinal cord damage [4]. Patients with TBI in early period frequently have arterial hypotension, which requires usage of sympatomimetics [5]. Fluid-resistant arterial hypotension can occur in patients with brain edema and without evidence of brainstem or spinal cord injury [6–8]. Hypothalamic nuclei can be damaged in this scenario, but it is not a well-documented cause of hypotension. Experimental data show the possibility of development of arterial hypotension after isolated damage of hypothalamus [9–21]. In this study we attempted to better characterize the clinical syndrome of arterial hypotension in patients following surgery for sellar region tumors.

Materials and Methods

Local ethics committee approved the study (number of the investigation is RK VNTITs 0120.0 504351).

A series of cases with clinical syndrome of arterial hypotension in the early postoperative period after sellar were prospectively investigated. All patients were admitted to neurological ICU (NICU) at Burdenko Neurosurgical Research Institute between May 2003 and December 2005. Inclusion criteria were: tumor of sellar region, and fluid-resistant arterial hypotension, which required usage of sympatomimetics during the early postoperative period (7 days). There were 15 patients taken from 1005 patients who were operated during the investigation period.

Demographic characteristics, description of tumors' histological type, neurological, endocrine status of patients before operation, and data about concomitant diseases are available in Table 1. Part of patients' preparation for surgery were correction of endocrine insufficiency and maintenance of normal fluid balance and correction of diabetes insipidus.

Surgical events are shown in Table 2. Intraoperative hemorrhage did not exceed 15% of the blood volume, and it was adequately corrected during operation. Intraoperative infusion therapy was aimed to achieve normovolemia under monitoring of CVP measurement using central venous catheter, hemoglobin, and hematocrit levels.

Table 1 Patient characteristics ($N = 15$)

Demographic characteristics
Age (years): 33–66 (median 50)
Males: 10 (67%)
Females: 5 (33%)
Histological characteristic of tumor[a]
Pituitary adenoma: 7 (47%)
Craniopharyngioma: 6 (40%)
Others 2[b]: (13%)
Neurological status before operation
Chiasmatic syndrome: 14 (93%)
Mental disorders: 6 (40%)
Pyramidal signs: 2 (13%)
Endocrinology status before operation
Secondary hypocorticism and hypothyroidism: 6 (40%)
Need for replacement therapy, including desmopressin acetate: 7 (47%)
Concomitant medical diseases
Essential hypertension: 11 (73%)

[a] In the total number of patients (1005 patients), adenomas corresponded to 74%, craniopharyngiomas: 14%, and other tumors: 12%. Thus, most cases with arterial hypotension among 1005 patients were associated with craniopharyngiomas

[b] Meningioma of sellar region and paraganglioma of sellar region

Table 2 Surgical events

Surgical approach
Subfrontal: 5 (33%)
Pterional 2: (13%)
Transcallosal: 1 (7%)
Combined—pterional and transcallosal: 3 (20%)
Transsphenoidal: 4 (27%)
Extent of tumor removal
Total removal: 4 (27%)
Subtotal removal: 6 (40%)
Partial removal: 5 (31%)
Damage of pituitary stalk
Pituitary stalk surgically cut or destroyed with tumor: 4 (40%)
Pituitary stalk saved: 9 (60%)
Urgent surgical interventions during first 7 days after tumor removal
Removal of tumor bed hematoma: 1 (7%)
External ventricular drainage due to hemorrhage: 2 (13%)

Hemodynamics were stable during operation. Coagulopathy was absent. All patients were anesthetized with propofol (45 mkg/kg/min), fentanyl (0.03 mkg/kg/min), and inhalation of nitrous oxide ($N_2O:O_2 = 3:1$).

Postoperatively and before arterial hypotension development baseline fluid management was 1.6 ± 0.3 ml/kg/h intravenously and 10–15 ml/kg per day enterally. Noninvasive monitoring of hemodynamics including echocardiography was performed.

Invasive hemodynamic monitoring with pulmonary artery catheter (PAC) and catheterization of radial artery was performed in 30 min after arterial hypotension onset in all cases. Hemodynamic profiles were measured every 6 h or when clinically needed. All PAC-derived hemodynamic measurements were recorded during the first 72 h after the onset of hypotension. Echocardiographic investigations were performed, but therapy was determined by invasive monitoring data. Generally echocardiographic data were similar to PAC results.

Statistical Analysis

We found normal of distribution of values with Lilliefors probabilities at every point of time. We used nonparametric methods, because the data incompletely corresponded to normal distribution. We used Friedman ANOVA for the determination of discrepancy significance. When we found discrepancy in Friedman ANOVA test we used Mann–Whitney U and Wald–Wolfowitz tests for specification discrepancies between data at different points of time. Data are presented as mean $\pm$ SD ($m \pm \delta$). Logarithmic approximation is made when needed. We used Statistica v. 6.0.

Results

All our tumors were large or giant (in our Institution classification tumor of sellar region is giant if its size exceeds 60 mm, and large when more than 35 mm) with infiltrative growth and invasion of the floor of the III ventricular. There was an intention to perform a total resection of sellar region tumors. Total tumor removal from the third ventricular was attempted in all cases. Data about extent of tumor resection are presented in Table 2. Causes of injury of hypothalamic nuclei and its frequency are given in Table 3.

Arterial hypotension developed in the early postoperative period in all cases (Table 4). At the time of arterial hypotension onset patients had APACHE II scale 25–27. In seven cases arterial hypotension developed on the first postoperative day. These patients did not recover after operation (Table 5). Fatal outcome was found in three patients (Table 4). Four cases recovered in 5 ± 2 days after correction of arterial hypotension.

In eight cases arterial hypotension developed 2–7 days after operation. These patients recovered after operation. Features of patients' condition at the time of arterial hypotension are presented in Table 5. Linear velocity of blood flow, measured with transcranial Doppler, was normal in all cases. Five patients died and three had a favorable outcome in this subgroup (Table 4).

Mechanism of fluid-resistant arterial hypotension after resection of sellar region tumor consists in marked decrease of vascular tone and development of relative hypovolemia. Signs of cardiac failure were not found.

Decrease of vascular tone was confirmed with monitoring of the index of systemic vascular resistance (SVRI), which was reduced during the entire period of invasive hemodynamic monitoring. A trend toward of increasing SVRI was observed during the investigation (Fig. 1). SVRI increased from 1503.3 ± 623.5 dyn·s·cm^5·m^2 at the start of the study, and during arterial hypotension development to 1747.47 ± 417.2 dyn·s·cm^5·m^2.

Selective α-sympatomimetics were used to treat hypotension, and unusally phenylephrine. Its dose (Fig. 2) was determined by SVRI and mean ABP.

Hypovolemia was confirmed because central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) were decreased. The combination of these data with severe decrease of SVRI suggested relative hypovolemia. During the invasive monitoring period both CVP and PAOP were increased. CVP significantly rose from 4.5 ± 2.6 to 6.8 ± 3.5 torr (Fig. 3). PAOP increase was statistically insignificant (from 8.1 ± 3.5 to 11.9 ± 3.5 torr). During the period of arterial hypotension, all patients received fluids 6.3 ± 1.9 ml/kg/h, pressors (phenylephrine: 1.2 ± 1.1 mcg/kg/min [minimum level], 4.6 ± 3.4 mcg/kg/min [maximum level] and dopamine 6.5 ± 0.8–7.5 ± 1.3 mcg/kg/min), and hormonal therapy, (recommended for patients with hormonal insufficiency in

Table 3 Cause of diencephalic damage

Cause of damage	Quantity
Infiltration of the floor of III ventricular with tumor and/or its growth into the cavity of III ventricular before operation	15 (100%)
Intraoperative tumor separation from the floor of III ventricular	7 (47%)
Attempt of total tumor removal from the third ventricular	15 (100%)

Table 4 Onset time of arterial hypotension development and outcomes

Postoperative day	Quantity	Outcomes
1st	7 (47%)	Lethal outcome in 3 cases
2nd	3 (20%)	Lethal outcome in 2 cases
3rd	1	Recovered
4th	1	Died
5th	1	Died
6th	1	Recovered
7th	1	Died

Table 5 Features of patients' condition on the moment of arterial hypotension development

Neurological status
Coma (GCS 5–7): 15 (100%)
Stereotypic unpurposeful activity and episodes of motor agitation: 9 (60%)
Secondary brain stem syndrome[a]: 15 (100%)
Presence or worsening of motor hemiparesis: 6 (40%)
Medical status
Mechanical ventilation: 15 (100%)
Dynamic ileus: 6 (40%)
Diabetes insipidus: 15 (100%)
Hyperglycemia: 15 (100%)
Hyperthermia[b]: 11 (73%)
Hypothermia: 4 (27%)
CT scan
Brain edema: 9 (60%)
Blood found in tumor bed: 7 (47%)
Intraventricular hemorrhage: 2 (13%)
Hemorrhage in tumor bed: 1 (6.5%)

[a] Secondary brain stem syndrome: miosis, horizontal and vertical divergent strabismus, absent light response, and lack of reflective upward gaze

[b] Sepsis was excluded in all cases

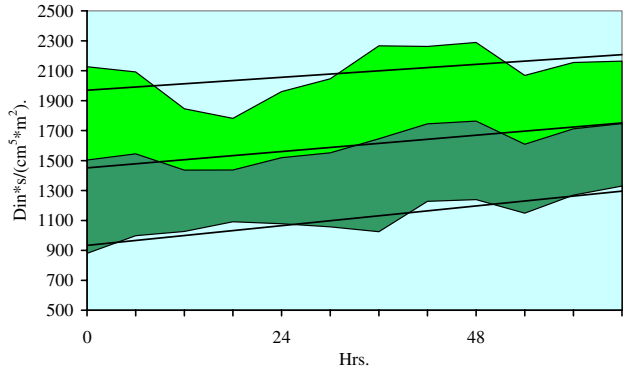

Fig. 1 Trends of mean values ± SD of SVRI. Normal ranges are 1970–2390 dyn s/(cm^5 m^2). Data are presented as mean ± SD (m ± δ). Logarithmic approximation is made for every index. SVRI was significantly less, than normal values, at the beginning of the investigation: 1503.3 ± 623.5 dyn s/(cm^5 m^2) (m ± δ). There was a significant increase of SVRI by 72nd hour of the investigation: 1747.47 ± 417.2 (m ± δ)

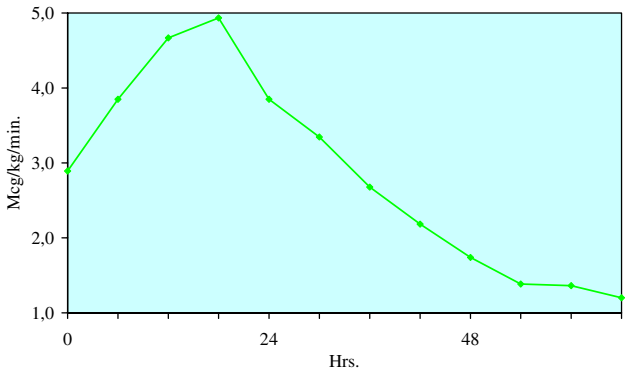

Fig. 2 Trends of mean values of phenylephrine doses. Recommended doses are 0.5–5 mcg/kg/min. Data are presented as mean (m). Maximal average phenylephrine dose was 4.9 mcg/kg/min. This dose had to be used at the end of the first investigation day. By the end of the investigation average phenylephrine dose fell to 1.2 mcg/kg/min

conditions of severe stress). Dose of hydrocortisone was 400–500 mg per day; dose of L-thyroxin was 2–3 μg/kg/day; and dose of desmopressin acetate was 0.2–0.8 mg per day (Table 6). Hormone levels were investigated once a day during the 72-h period of the survey (Table 6).

Infusion therapy was guided by dynamic control of levels of CVP and PAOP that allowed us to use the highest possible dose of infusion. On average, daily total quantity of fluid was 7000–8000 ml, but occasionally it achieved 15,000–16,000 ml per day in cases of severe diabetes insipidus or considerable hypovolemia due to another cause (Fig. 4).

Myocardial contractility was not impaired. Stroke index (SI) was normal or increased in all cases during the entire period of invasive monitoring. It reached 53.8 ± 13.3 ml/m^2 at the beginning of the investigation and

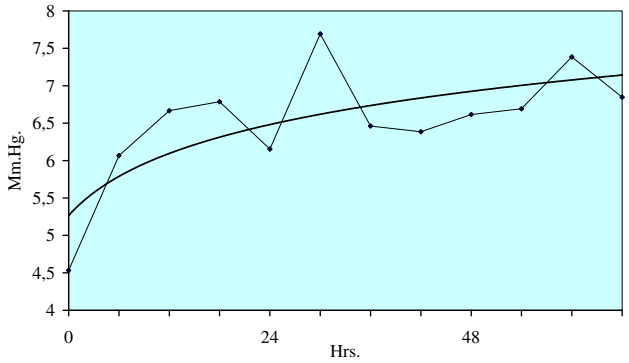

Fig. 3 Trends of average values of CVP. Normal ranges are 8–10 mmHg. Data are presented as mean (m). Logarithmic approximation is shown. Mean CVP was 4.5 mmHg at the beginning and it increased to 6.8 mmHg after 72 h of the investigation

54.2 ± 12.8 ml/m^2 at the end of invasive monitoring period.

Average value of cardiac index (CI) in the whole group did not change during the investigation. CI was normal or increased (beginning of investigation: 4.4 ± 1.6 l/min/m^2, end of investigation: 4.2 ± 0.8 l/min/m^2), but analysis of CI trends for every patient individually showed that four patients had slight reduction of CI (Fig. 5). The cause of CI decrease was severe bradycardia. This phenomenon was not very common and developed only in four cases (Fig. 6). Bradycardia was always combined with hypothermia and dynamic ileus. These symptoms are typical for severe hypothyroidism. Since bradycardia was regarded as sign of decompensated hypothyroidism, β-sympathomimetics were used. Major feature of therapy with thyroid hormone was combination of T_4 with T_3. Thyroid hormone levels in plasma and dose of hormonal agents are presented in Table 6. Hypothyroidism was largely diagnosed clinically, because diagnostic value of plasma hormone level is less useful with thyroid therapy. The β-sympathomimetics dopamine was used in dose 4–9 mcg/kg/min. Exact dose was determined levels of CI and heart rates (HR). Dopamine was used in four cases increased until the dose of thyroid hormone normalized CI and HR.

Management described above led to normalization of arterial blood pressure (Fig. 7).

Mortality was 53%. The outcome was fatal in three cases during 1–28 days period and lethal in five cases above 28 days after operation. Causes of death were verified at autopsy and are shown in Table 7.

Discussion

The clinical phenomenon of fluid-resistant arterial hypotension after sellar region tumor is very uncommon.

Table 6 Used hormonal drugs and plasma levels

Hormone	1st day	2nd day	3rd day
Hormonal agents used			
Hydrocortisone (mg)	549.5 ± 522.9	529.2 ± 131.8	529.2 ± 131.8
Dexamethasone (mg)	12.8 ± 3.1	12.9 ± 3.3	12.9 ± 3.3
L-thyroxin (mcg)	206.7 ± 25.8	215.4 ± 24	200 ± 35.4
Desmopressin (mg)	0.92 ± 1.15	0.61 ± 0.57	0.48 ± 0.26
Hormone levels in plasma			
T_3	1.23 ± 1.06	1.04 ± 0.89	0.72 ± 0.47
T_4	87.4 ± 28.8	72.5 ± 15.6	74.8 ± 32.1
Free T_3	2.61 ± 0.76	2.21 ± 1.23	2.91 ± 0.86
Free T_4	14.01 ± 3.37	16.43 ± 3.91	15.71 ± 1.37
Cortisol	458.1 ± 374.1	661.5 ± 444.1	787.3 ± 481.9
Renin	0.98 ± 0.27	0.65 ± 1.26	0.67 ± 0.44
Aldosterone	12.29 ± 5.72	26.53 ± 22.49	22.49 ± 8.08

Dexamethasone was used for anti-edematous therapy after craniotomy in neurooncology patients. Hydrocortisone was used in patients with secondary/tertiary adrenal insufficiency. T_3 (normal range: 1.2–2.8 nmol/l); T_4 (normal range: 55–170 nmol/l); Free T_3 (normal range: 2.76–6.45 pmol/l); Free T_4 (normal range: 10.1–22 pmol/l); Cortisol (normal range: 350–690 nmol/l); Renin activity (normal range: 0.5–1.9 ng/ml/h); Aldosterone (normal range: 27.7–291.3 pmol/l); Data are presented as mean ± SD (m ± δ)

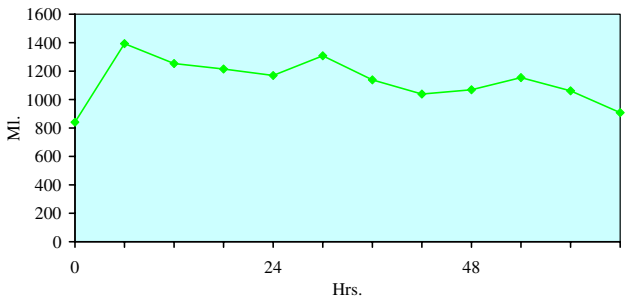

Fig. 4 Trends of average values of fluid balance. Fluid balance was calculated as a difference between input and output during the 4-h period. Data are presented as mean (m). Fluid balance was positive during entire investigation period

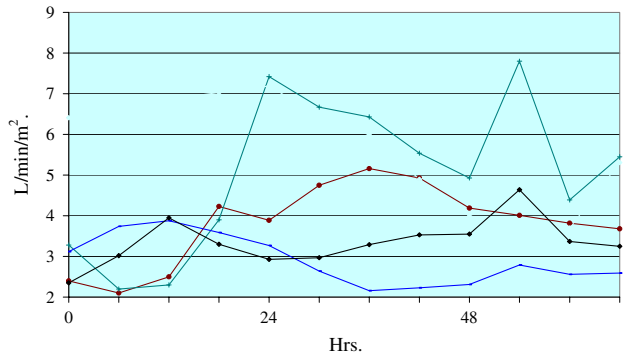

Fig. 5 Trends of CI of four cases with CI abnormalities. Normal ranges are 2.5–4.0 l/min/m^2. Data are presented as absolute values. CI was discussed in four cases at different times of the investigation. These patients required infusion of β-sympathomimetics (dopamine in β-sympathomimetic doses: 4–9 mcg/kg/min)

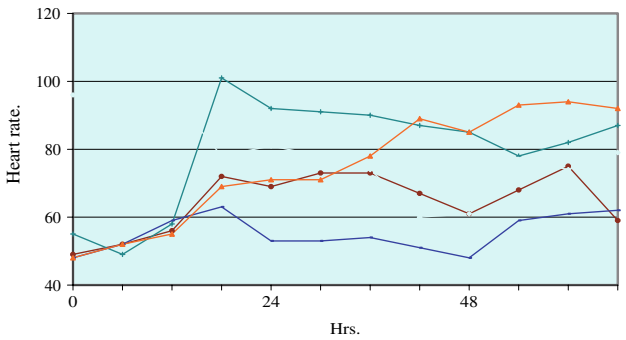

Fig. 6 Trends of heart rates in patients with bradycardia. Normal ranges are 60–90 per min. Data are presented as absolute values. HR was less than normal values in four cases. These patients required infusion of β-sympathomimetics (dopamine in β-sympathomimetic doses: 4–9 mcg/kg/min)

According to our data, it develops in approximately 1.5% patients in early postoperative period. However, it is a major cause of death. This prompted us to further study this phenomenon.

A search for clinical studies in MEDLINE was unsuccessful. On the other hand, there are several experimental studies, which investigated hemodynamic response after a variety of injury to hypothalamic nuclei [11–14, 16, 18, 19, 21]. It is known that paraventricular nuclei and zone AV_3V, which is located at the anterior part of the III ventricle, exert the most considerable influence over systemic hemodynamics [9, 10, 17, 20]. Hilton studied hemodynamic response after electrical irritation of perifornical area and anterior nuclei of hypothalamus in cats [15]. There were two types of hemodynamic response. The

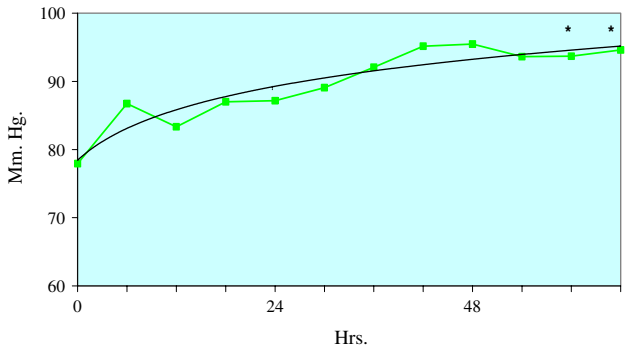

Fig. 7 Trends of average values of mean arterial pressure. Normal ranges are 70–110 mmHg. Data are presented as mean (m). Logarithmic approximation is shown. Mean arterial pressure increased during the period of the investigation. * Values significantly differed from the beginning of the investigation ($P < 0.05$)

Table 7 Causes of death

In the period 1–28 days after operation
Ischemic insult at diencephalon: 1
Intraventricular hemotamponade: 2
In the period after 28 days from operation
Sepsis[a]: 4
Pulmonary embolism: 1

[a] Sepsis occurred 3 weeks after surgery

first one, which developed more frequently, consisted in diffuse vasoconstriction and arterial hypertension. The second response was distinguished by diffuse vasodilatation and severe arterial hypotension. Massive release of catecholamines from adrenals subsequently stabilized the blood pressure.

The mechanism of arterial hypotension in our study population consists of severe decreased vascular tone due to vasodilatation. All our patients had tumors which theoretically could impact diencephalon region directly or there was tumor growth with infiltration of floor of third ventricular and its cavity. Other causes of fluid-resistant arterial hypotension in our patients could be adrenal insufficiency, injury of caudal brainstem, or inhaled anesthetics. Injury of brainstem was not confirmed with MRI or autopsy.

Theoretically, nitrous oxide can result in vasodilatation and arterial hypotension. However, in practice, it is unlikely that nitrous oxide could result in resistant arterial hypotension. First, nitrous oxide has minimal influence to vascular tone [22]. Secondly, it is unlikely that nitrous oxide would be a cause of hypotension that requires infusion of phenylephrine in high doses (maximal average dose was 4.9 mcg/kg/min). Thirdly, half-life of nitrous oxide is 5 min [23, 24]. In one patient, arterial hypotension developed in the first postoperative day in 7 patients and in the period 2nd to 7th day in 8 patients.

One could surmise that decompensated adrenal insufficiency can be an immediate cause of such severe fluid-resistant arterial hypotension. Besides, decompensated adrenal insufficiency inevitably lead to hyponatremia, hyperkalemia, and hypoglycemia. However, our patients had different homeostatic disturbances. Moreover, every patient received hydrocortisone in high dose. In such conditions only relative adrenal insufficiency can occur. We doubt that relative adrenal insufficiency cannot be an immediate cause of such severe fluid-resistant arterial hypotension. Diencephalon injury as an immediate cause of arterial hypotension can be implicated because neurological deterioration preceded development of arterial hypotension.

Our clinical model and Hilton's experimental study are similar. The major difference is the lack of compensation due to massive release of catecholamines from adrenals in our patients. This is not surprising because our patients had compromised adrenals due to secondary adrenal insufficiency (40% before operations and theoretically 100% after operation; all patients received hormonal therapy with hydrocortisone after operation) (Table 6). Hydrocortisone in doses, which we employed, prevents adrenal crises or development of decompensated adrenal insufficiency, but evidently it is not able to compensate in a critical setting. Thus, we are faced with the question whether the dose of glucocorticoids is adequate. Further investigations are necessary to answer this complex question.

α-Sympatomimetics were used after determination of the mechanism of arterial hypotension. Routine use of β-sympatomimetics was unsuitable because myocardial contractility was normal or increased. This was an unexpected result because we expected fluid-resistant arterial hypotension after sellar region tumor resection was due to cardiac failure. Prior data as shown the possibility of cardiomyopathy in patients with sellar region tumor, especially in patients with pituitary adenoma and acromegaly [25, 26].

β-sympatomimetics must be used as symptomatic therapy for stabilization of CI and HR before adequate dose of thyroid hormone can be used. Low T_3 syndrome is common in critical care patients [27–29]. Perhaps this syndrome is the cause of bradycardia which develops during α-sympatomimetics usage. In our study bradycardia occurred during phenylephrine usage only in patients with decompensated hypothyroidism. On the other hand, bradycardia did not develop in patients without signs of hypothyroidism, even when the dose of phenylephrine was extremely high (11–11.5 μg/kg/min). However, our patient population is very small and we can only speculate about this mechanism.

We used high volumes of infusion therapy and this treatment was successful. However, it would be very possibly hazardous to use high volumes without Swan-Ganz monitoring. Recently, some authors cast doubt on efficacy of pulmonary catheterization to outcomes [30]. However, we could not safely implement such aggressive infusion therapy without Swan-Ganz monitoring. Others, however, presented better outcomes in patients monitored with pulmonary catheterization, especially if patients had severe conditions (APACHE II > 22–24) [31, 32].

Conclusion

Hypothalamic damage can be an immediate cause of fluid-resistant arterial hypotension. We did not find other plausible causes of fluid-resistant arterial hypotension after sellar tumor resection. The mechanism of resistant arterial hypotension consists in decrease of vascular tone and relative hypovolemia and responds to sympatomimetics. β-sympatomimetics are indicated in cases with thyroid insufficiency as symptomatic therapy. Simultaneously, dose of thyroid hormone should be increased. Further research is needed to better understand risk factors for this syndrome, and to reduce the high mortality rate associated with this disorder.

Acknowledgment We thank Mr. V.I. Lukianov for his support in performing the statistic analysis.

References

1. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34:216–22.
2. Guidelines for the Management of Severe Traumatic Brain Injury. 3rd ed. Brain Trauma Foundation; 2006. p. 10–9.
3. Suarez JI. Critical care neurology and neurosurgery. Humana Press; 2003. p. 138, 143.
4. King BS, Gupta R, Narayan RK. The early assessment and intensive care unit management of patients with severe traumatic brain and spinal cord injuries. Surg Clin North Am 2000;80:855–70.
5. Zygun DA, Doig CJ, Gupta AK, et al. Non-neurological organ dysfunction in neurocritical care. J Crit Care 2003;18:238–44.
6. Chun-Chang Y, Ching-Tang W, Chueng-He L, et al. Use of small-dose vasopressin for unstable hemodynamics in an acute brain injury patient refractory to catecholamine treatment: a case report. Anesth Analg 2003;97:577–9.
7. Kolin A, Norris JW. Myocardial damage from acute cerebral lesions. Stroke 1984;15:990–3.
8. Macmillan CSA, Grant IS, Andrews PJD. Pulmonary and cardiac sequelae of subarachnoid hemorrhage: time for active management? Intensive Care Med 2002;28:1012–23.
9. Bealer SL. Vascular capacitance following preoptic recess lesions. Am J Physiol Heart Circ Physiol 1993;264:H560–6.
10. Brody MJ, Johnson AK. Role of the anteroventral third ventricle region in fluid and electrolyte balance, arterial pressure regulation, and hypertension. In: Martini L, Ganong WF, editors. Frontiers, neuroendocrinology. New York: Raven; 1980. p. 249–92.
11. Cabrera C, Bohr D. The role of nitric oxide in the central control of blood pressure. Biochem Biophys Res Commun 1995;206:77–81.
12. Diz DI. Bradykinin and related peptides in central control of the cardiovascular system. Peptides 1985;6:57–64.
13. Harfstrand A. Intraventricular administration of neuropeptide Y (NPY) induces hypotension, bradycardia and bradypnoea in the awake unrestrained male rat. Counteraction by NPY-induced feeding behaviour. Acta Physiol Scand 1986;128:121–3.
14. Harland D, Bennett T, Gardiner SM. Cardiovascular actions of neuropeptide Y in the hypothalamic paraventricular nucleus of conscious Long Evans and Brattleboro rats. Neurosci Lett 1988;85:239–43.
15. Hilton SM. Hypothalamic regulation on the cardiovascular system. Br Med Bull 1966;22:243–8.
16. Horn T, Smith PM, McLaughlin BE, et al. Nitric oxide actions in paraventricular nucleus: cardiovascular and neurochemical implications. Am J Physiol Regul Integr Comp Physiol 1994;266:R306–13.
17. Lind RW. Angiotensin and the lamina terminalis: illustrations of a complex unity. Clin Exp Hypertens A 1988;10:79–105.
18. Nakata T, Berard W, Kogosov E, et al. Microdialysis in the posterior hypothalamus: sodium chloride affects norepinephrine release, mean arterial pressure, heart rate and behaviour in awake rats. Brain Res Bull 1990;25:593–8.
19. Philippu A, Dietl H, Sinha JN. In vivo release of endogenous catecholamines in the hypothalamus. Naunyn-Schmiedebergs Arch Pharmacol 1979 308:137–42.
20. Smith PM, Ferguson AV. Vasopressin acts in the subfornical organ to decrease blood pressure. Neuroendocrinology 1997;66:130–5.
21. Stryker WS, Boudier HAJ, Smeets GWM, Brouwer GM, et al. Hypothalamic alpha adrenergic receptors in cardiovascular regulation. Neuropharmacology 1974;13:837–46.
22. Turner DM, Kassell NF, Sasaki T, et al. Time-dependent changes in cerebral and cardiovascular parameters in isoflurane-nitrous oxide-anesthetized dogs. Neurosurgery 1984;14:135–41.
23. Cho S, Fujigaki T, Uchiyama Y, et al. Effects of sevoflurane with or without nitrous oxide on human cerebral circulation: transcranial doppler study. Anesthesiology 1996;85:755–60.
24. Wilson-Smith E, Karsli C, Luginbuehl I, et al. Effect of nitrous oxide on cerebrovascular reactivity to carbon dioxide in children during sevoflurane anesthesia. Br J Anaesth 2003;91:190–5.
25. Hashimoto K, Yamanaka M, Uschida H, et al. A patient with acromegalic heart disease – a case report. Masui 1997;46:951–4.
26. Lie JT, Grossman ST. Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients. Am Heart J 1980;100:41–52.
27. Sumita S, Ujike Y, Namika A, et al. Suppression of the thyrotropin response to thyrotropin-releasing hormone and its association with severity of critical illness. Crit Care Med 1994;22:1603–9.
28. Novitzky D, Cooper DK, Barton CI, et al. Triiodothyronine as an inotropic agent after open heart surgery. J Thorac Cardiovasc Surg 1989;98:972–8.
29. Novitzky D, Cooper DK, Morrell D, et al. Change from aerobic to anaerobic metabolism after brain death, and reversal following triiodothyronine therapy. Transplantation 1988;45:32–6.
30. Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996;276:889–97.

31. Boyd O, Bennett D. Enhancement of perioperative tissue perfusion as a therapeutic strategy for major surgery. New Horiz 1996;4:453–65.

32. Chittock DR, Dhingra VK, Ronco JJ, et al. Severity of illness and risk of death associated with pulmonary artery catheter use. Crit Care Med 2004;32:911–5.