An interesting and instructive case report on neurogenic pulmonary oedema (NPE) is published in this issue of the NJCC [1]. The patient suffered from cerebellar haematoma, secondary acute hydrocephalus, ECG abnormalities (bradycardia, tachycardia, ST-segment depression, inverted T-waves, and ventricular extrasystoles), global left ventricular dysfunction, elevated serum CK-MB and troponin levels, hypotension and lung oedema. Initial treatment included mechanical ventilation with high positive end expiratory pressure (PEEP), volume loading, atropine and norepinephrine. Later on the patient received dobutamine “to treat a possible cardiogenic component of the pulmonary oedema”. Oxygenation improved during the prone positioning required for the surgical removal of the cerebellar haematoma. This case report illustrates the dangerous cardiopulmonary sequelae in acute neurological disease. We will elaborate on the role of intracranial pressure (ICP) in the cardiopulmonary complications of intracranial catastrophes and the effect of volume loading and norepinephrine on the cardiac performance in these conditions.

The ICP is acutely and severely elevated in subarachnoid haemorrhage (SAH), in traumatic brain injury with intracranial haemorrhage or non-traumatic intracranial haemorrhage and cerebral blood flow (CBF) drops to the extent that it evokes cerebral ischaemia. Then, the vasoconstrictor and cardio-accelerator neurons in the vasomotor centre (located in the lower pons and medulla) become immediately and strongly excited, i.e. the central nervous system ischaemic response of the Cushing type [2]. Obviously, the vigorous Cushing reaction is the most powerful protective measure against deteriorating cerebral ischaemia [2]. But, if the Cushing reaction is accompanied by neurogenic myocardial stunning and left ventricular dysfunction, high blood pressure is the result of extreme vasoconstriction with low cardiac output. High blood pressure with diminished cardiac performance may still help to perfuse the organs, including the brain, with high vascular resistance and with low blood flow [13]. In the case report by Stessel, et al. [1], globally reduced left ventricular function was confirmed by echocardiography. Apparently, cardiac performance was severely affected to the extent that blood pressure dropped. The first steps reported after intubation were volume loading and norepinephrine administration [1].

Volume loading leads to higher filling pressure and preload of the right ventricle, and to augmentation of right ventricular end diastolic volume (RVEDV) [13-16]. Increased RVEDV may elicit competition for pericardial diastolic volume between right and left ventricles causing impaired diastolic filling of the left ventricle and further deterioration of left ventricular performance [16]. Moreover, volume loading leads to haemodilution (decreased haematocrit), and cardiac performance increases to compensate for the lower viscosity [14,17,18], but the failing heart cannot meet the demand for increased cardiac performance.

Administration of norepinephrine in patients with Cushing re-
action and reduced left ventricular performance will further increase vascular resistance, arterial blood pressure, and systolic myocardial wall stress and afterload, reducing left ventricular performance [13-15]. In addition, norepinephrine increases right ventricular filling pressure and preload through decreased systemic vascular volume due to vasconstriction [2,13-15].

Therefore, administration of volume loading and norepinephrine in patients with neurogenic myocardial stunning and NPE leads to further impairment of cardiac performance and possibly to worsening of NPE. On the other hand, it is known that \( \beta_2 \) AR agonists, phosphodiesterase inhibitors [8,10] and myofilament Ca\(^{2+} \) sensitizers [19] can recruit the inotropic reserve of the stunned myocardium and improve cardiac performance. Recently, improvement of cardiac output [9,11,12] and resolution of pulmonary oedema [11,12] were reported in small series of patients with neurogenic myocardial stunning and NPE after administration of dobutamine or milrinone.

Fortunately, in the case report by Stessel, et al. [1] in this issue, additionally to surgical decompression of the cerebellum and brainstem, volume loading and norepinephrine, dobutamine was added to the therapeutic regimen. Moreover, the authors applied PEEP. Besides a positive effect in blood oxygenation due to improved ventilation-perfusion ratio, PEEP reduces the venous return and therefore reduces RVEDV, preload and the competition for pericardial diastolic volume between right and left ventricles [16]. PEEP also decreases the transmural pressure of the left ventricle, reducing ventricular wall stress and by definition reducing afterload [15]. No need to say that thereafter, the stunned heart beats more efficiently, the clouded lungs brighten swiftly, and the struck “mind bearer” may be rescued.

We conclude that in patients with acute neurological disease with an intracranial mass lesion, complicated by myocardial dysfunction and NPE, early neurosurgical evacuation of the mass lesion should be performed whenever possible. Medical treatment must be aimed at restoring cerebral blood flow rather than isolated arterial blood pressure augmentation and isolated pulmonary oedema treatment. This medical treatment includes restoration of cardiac performance and oxygen transport to the brain (by means of volume loading, administration of \( \beta_2 \) AR agonist or phosphodiesterase inhibitor and mechanical ventilation with PEEP) and elevation of blood pressure to ensure adequate perfusion pressure of the brain (by norepinephrine).

**Table.** Effect of extremely elevated intracardial catecholamine levels on ventricular contractility (modified table originated from Kassim, TA, et al. 2008 [5]).

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>MECHANISM</th>
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<tbody>
<tr>
<td>Receptor-mediated negative inotropic effect of extremely elevated catecholamine levels</td>
<td>Epinephrine binds to ( \beta_2 ) adrenergic receptors (( \beta_2 ) ARs) of myocytes, through Gs protein signaling activation of adenyl cyclase, which increases intracellular cyclic AMP levels. This activates protein kinase A (PKA) and phosphorylates several intracellular targets resulting in an increased contractile response [6]. In “supraphysiological” epinephrine concentrations in the heart tissue, a switch in signal trafficking from ( \beta_2 ) AR-Gs protein to ( \beta_2 ) AR-G1 protein coupling is initiated. Stimulation of ( \beta_2 ) AR-G1 protein signaling pathways has been shown to produce a negative inotropic effect on human ventricular myocytes [6]. This does not apply for norepinephrine, because norepinephrine does not activate the ( \beta_2 ) ARs.</td>
</tr>
<tr>
<td>Direct toxic effect of catecholamines and their oxidation products</td>
<td>Increased permeability of sarcocellular membrane. Increased cytosolic concentration of calcium (calcium overload) followed by decreased myofilament responsiveness to calcium [8].</td>
</tr>
<tr>
<td>Excessive ( \alpha ) adrenergic stimulation attributable to extremely elevated catecholamine levels</td>
<td>Intense vasconstriction and coronary vasospasm. Subendocardial myocardial ischaemia and subsequent irreversible subendocardial damage and necrosis.</td>
</tr>
</tbody>
</table>
Treat, but meanwhile do not harm. Neurogenic myocardial dysfunction and pulmonary oedema

References