Novel treatment (new drug/intervention; established drug/procedure in new situation)

High-dose insulin therapy for neurogenic-stunned myocardium after stroke

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Summary

A 44-year-old woman with a history of complicated type 2 diabetes mellitus presented with a diagnosis of right-hemispheric ischaemic stroke. She developed acute respiratory distress with radiological evidence of pulmonary oedema. The ECG showed poorly significant ST-segment changes, with a minimal increase of cardiac biomarkers. Echocardiography showed a severely depressed left ventricular function, with also low values of cardiac output at invasive monitoring. The possibility of neurogenic-stunned myocardium was discussed and a metabolic resuscitation with high-dose insulin was proposed. An intravenous bolus of 80 units of insulin (0.72 IU/kg) was followed by a continuous infusion at the rate of 160 IU/h (1.45 IU/kg/h). The treatment led to a rapid and sustained improvement of the haemodynamic condition and was well tolerated. In comparison with dobutamine, insulin had significant inotropic effects without tachycardia. The patient unfortunately died on day 35, from respiratory complications after poor neurological recovery.

BACKGROUND

Neurogenic-stunned myocardium is an entity that has been described mainly after subarachnoid haemorrhage (SAH). This complication has been exceptionally reported after ischaemic or haemorrhagic stroke, but is probably underestimated. There is probably some overlap between neurogenic-stunned myocardium and takotsubo cardiomyopathy, with excessive sympathetic stimulation as a common underlying disorder. As there is a high suspicion of catecholamine-mediated cardiotoxicity, the treatment of the severe forms of neurogenic-stunned myocardium with acute left ventricular dysfunction should avoid the administration of exogenous catecholamines. There is an increasing interest for the inotropic and vasodilatory properties of high doses of insulin. This observation illustrates the potential benefit of high doses of insulin as first line therapy in a case of a stroke-associated cardiogenic shock. In particular, high doses of insulin are not followed by the tachycardia that usually follows catecholamines administration, and could therefore prevent excessive myocardial oxygen consumption.

CASE PRESENTATION

A 44-year-old woman was admitted in the emergency department (ED) for acute left hemiplegia and respiratory distress. The symptoms started 120 min before hospital admission. She had a medical history of metabolic syndrome, morbid obesity (110 kg body weight, body mass index 43), dyslipidaemia, arterial hypertension and type 2 diabetes mellitus complicated by retinopathy, macroalbuminuria with preserved renal function and peripheral macroangiopathy. There was no history of atrial fibrillation. A recent carotid angiography has disclosed a non-significant stenosis (<30%) of the right internal carotid. Cardiac investigations had been performed one year before admission. The left ventricular function was well

preserved at echocardiography (shortening fraction 44%). There was no evidence for myocardial ischaemia at myocardial perfusion scintigraphy (submaximal MIBI stress test).

INVESTIGATIONS

Upon admission in the ED, the diagnosis of right-hemispheric stroke was supported by the clinical findings (right gaze deviation, left hemiplegia, hypoesthesia and spatial neglect). The brain CT, performed 196 min after symptoms onset, failed to reveal acute ischaemic lesions. Due to progressive dyspnoea, orotracheal intubation was required for mechanical ventilation. The chest angio-CT ruled out pulmonary embolism.

According to the brain CT findings, to the National Institute of Health Stroke Scale score of 18 and to a delay lower than 4 h after symptoms onset, an intravenous thrombolysis (rt-PA) was performed. The patient was admitted in the neurological intensive care unit (NICU) with the following parameters: Glasgow Coma Scale of 7/15 (E1, V1, M5 R), arterial blood pressure 98/78 mm Hg, and HR 130 /min. Haemodynamic conditions worsened rapidly. Extremities were cold and cyanotic, systolic blood pressure decreased with a marked sinus tachycardia (>140 /min). Urine output significantly decreased. A continuous infusion of norepinephrine was started up to 33 µg/min. The ECG revealed sinus rhythm, 1 mm ST-segment depression in I and augmented vector left (aVL) leads, together with negative T waves. The worsening of hypoxaemia required the increase of inspired oxygen fraction (FiO₂) from 0.21 to 0.6. The chest x-ray was consistent with acute pulmonary oedema. The admission troponin-I concentration was 3.69 ng/ml (normal value <0.08) with a peak at 5.46 ng/ml 30 h later. The transoesophageal echocardiography (TEE) demonstrated that the left ventricular function was severely altered (left ventricle

ejection fraction 26%) with a relative preservation of the apical wall motion. There was no evidence for an intracardiac thrombus, nor for a patent foramen ovale. A Swan-Ganz catheter was inserted and revealed a cardiac output of only 1.9 l/min, with a mean pulmonary arterial pressure of 41 mm Hg, a pulmonary capillary wedge pressure of 23 mm Hg and a pulmonary artery venous saturation (SvO₂) of 49%.

DIFFERENTIAL DIAGNOSIS

Cardiogenic shock—myocardial infarction—neurogenic-stunned myocardium—takotsubo cardiomyopathy.

TREATMENT

According to a local experience of beneficial inotropic effects of high doses of insulin for myocardial stunning after SAH, we opted for this strategy instead of introducing standard inotropic agents.¹ Practically, the patient received an intravenous bolus of 80 units of fast-acting insulin (corresponding to 0.72 IU/kg body weight), followed by a continuous infusion at the rate of 160 IU/h (1.45 IU/kg/h). This was preceded by the injection of 30 g of dextrose, and a solution of dextrose 30% together with potassium supplementation was administered over the period of high-dose insulin infusion, with a strict monitoring of serum glucose and potassium. No episode of hypoglycaemia was recorded. The effects of insulin administration are shown in figure 1. Twenty minutes after insulin bolus, cardiac output rose from 1.9 to 2.6 l/min (corresponding to a 37% increase) and SvO₂ from 49% to 63%. Five hours after the start of insulin therapy, cardiac output was 4.9 l/min. The same insulin dosage regimen (160 IU/h) was continued for 19 h. During this period, cardiac output was maintained >4 l/min, HR between 85 and 108 bpm, arterial lactate <2 mmol/l. There was a significant improvement of urine output, a decrease of FiO₂

from 0.6 to 0.21 and a progressive weaning of norepinephrine infusion from 33 to 10 µg/min.

We decided to interrupt insulin infusion for 6 h (wash-out) and observed a decrease of cardiac output (figure 2). We tried to compare dobutamine to high-dose insulin and we found that we had to infuse dobutamine at the rate of 416 µg/min in order to achieve a comparable cardiac output and SvO₂. Interestingly, the HR under dobutamine therapy was significantly higher (90–137 bpm) in comparison with the values noted during insulin therapy. We were also able to estimate the total body oxygen consumption (VO₂) by indirect calorimetry during the two periods and found that dobutamine therapy was responsible for a 12% increase in O₂ consumption. Dobutamine therapy was progressively weaned over 72 h.

OUTCOME AND FOLLOW-UP

Further neurological outcome was poor with persisting left hemiplegia and a large right middle cerebral artery stroke on repeat brain CT. A tracheostomy was performed and the patient left the NICU on day 17. The repeat echocardiography at one-month follow-up showed a partial recovery of left ventricular dysfunction (ejection fraction 54%). It was initially planned to perform a coronary angiography before transferring the patient to the rehabilitation unit. Unfortunately, her neurological condition remained very poor and the patient died on day 35 from respiratory complications. An autopsy was proposed but refused by the relatives.

DISCUSSION

The term of 'neurogenic-stunned myocardium' (also described as stress or takotsubo cardiomyopathy) as usually refers to reversible left ventricular dysfunction that can occasionally be observed after SAH.^{1 2} This complication has been exceptionally reported after ischaemic

Figure 1 Evolution of cardiac index (CI) (equivalent to cardiac output divided by body surface area) and systemic vascular resistances (SVR) following insulin bolus and infusion at two different rates. No significant change was observed in HR. A further increase of CI was noted at the highest infusion rate, with a decrease of SVR.

Figure 2 Evolution of cardiac index (CI) and HR following continuous infusion of insulin at the rate of 160 IU/h. A withdrawal period of 6 h was then performed, with a subsequent decrease of CI. A continuous infusion of dobutamine was then introduced at the rate of 416 µg/min to achieve a cardiac index comparable to that obtained with high-dose insulin therapy. During this period, HR was significantly higher. Total body oxygen consumption (VO₂) was higher during the period of dobutamine treatment.

or haemorrhagic stroke, but is probably underestimated.^{3–6} Indeed, in the series published by Yoshimura *et al*,⁷ the incidence in patients with ischaemic stroke was 1.2%. Female sex and insular damage were predominant features of the stroke patients who experienced takotsubo cardiomyopathy. The insular cortex is regarded to contribute to cortical control of autonomic cardiac function.⁸ The differential diagnosis should obviously include a true acute coronary syndrome occurring simultaneously to the stroke. We cannot totally exclude in the present observation that rt-PA given for stroke could also have contributed to the recanalisation of a coronary vessel. The TEE failed to demonstrate a common embolic origin for both stroke and cardiac events. There was also a discrepancy among the limited and a specific ECG changes and the diffuse hypocontractility at echocardiography. We considered that neurogenic-stunned myocardium was the most likely diagnosis. Unfortunately, the integrity of the coronary arteries could not be assessed by angiography or by postmortem examination.

Classically, the takotsubo cardiomyopathy usually includes ECG changes mimicking acute myocardial infarction and minimal increase in cardiac biomarkers (troponin-I) contrasting with significant apical wall motion abnormalities at echocardiography. In contrast to the classical description of takotsubo syndrome involving the apical and distal walls of the left ventricle, variants of neurogenic-stunned myocardium have been described in SAH where the basal and middle ventricular portions of the anteroseptal and anterior walls are involved.^{9–10} While most of the patients will remain poorly symptomatic, some will develop acute heart failure. The pathophysiology of neurogenic stunned myocardium is not perfectly understood. A catecholamine-induced neurocardiogenic injury has been proposed as a causal factor and elevated circulating catecholamines levels have been observed in patients with stress cardiomyopathy.

Excessive exogenous catecholamines administration has also been shown to cause stress cardiomyopathy.¹¹ It has also been recently shown that the patients who were treated by β-blockers before the development of aneurysmal SAH were at lower risk to develop neurogenic-stunned myocardium.¹²

Neurogenic-stunned myocardium is by nature a reversible condition. When only a mild cardiac dysfunction is apparent with echocardiography (ejection fraction of ~40%), it seems logical to propose supportive therapy and wait for spontaneous recovery.¹ However, in patients with cardiogenic shock, inotropic medications (dobutamine or phosphodiesterase inhibitors) are often required to improve myocardial contractility.¹³ These drugs may have serious adverse effects including tachycardia, hypotension and increased myocardial oxygen demand. The metabolic resuscitation with insulin has been investigated for many years in cardiogenic shock.¹⁴ In both ischaemic and non-ischaemic shock, there is a diversion of myocardial metabolism from fatty acids to preferential carbohydrate oxidation and insulin could stimulate glucose myocardial uptake. It has been suggested that insulin could produce optimal effects in non-ischaemic cardiodepression, especially when associated with myocardial insulin resistance that could be related to excessive catecholamine stimulation.¹⁵ Moreover, recent works demonstrated that insulin at relatively high doses had positive inotropic properties that were independent from myocardial metabolism.¹⁶

In contrast to the publications dealing with the use of glucose-insulin-potassium in the setting of acute myocardial infarction, the experience with high-dose insulin for neurogenic-stunned myocardium is still limited.¹ As illustrated by the present observation, one of the potential advantages of insulin over catecholamines is a positive inotropic effect without tachycardia, thus limiting myocardial oxygen consumption.

There is no adopted protocol for high-dose insulin in this particular setting. In toxin-induced cardiogenic shock, most clinicians recommend an initial bolus of 1 IU/kg followed by a 0.5–1 IU/kg/h continuous infusion, but higher doses (up to 10 IU/kg/h) have been used in refractory cases. Patients should be supplemented with intravenous dextrose and potassium and should be monitored carefully. The major anticipated adverse events associated with high-dose insulin are hypoglycaemia and hypokalaemia. The onset of action of high-dose insulin has been stated as early as 15–45 min. The improvement in haemodynamic conditions should be assessed by monitoring mental status, skin warmth and colour, peripheral pulses, urine output and vital signs. Insulin as an inotrope and vasodilator has minimal effects on systolic blood pressure. There are currently no studies illustrating the best way to decrease high-dose insulin therapy after cardiac function has improved.

In conclusion, neurogenic myocardial stunning is possible after stroke. When the patient is extremely symptomatic, catecholamines are often the preferred drugs to improve cardiac function. However, the pathophysiology of stress cardiomyopathy clearly suggests that excessive sympathetic stimulation may have detrimental effects. In order for high-dose insulin to be of greatest benefit, it should be used early on in therapy rather than as rescue therapy.

Learning points

- ▶ Neurogenic-stunned myocardium is a rare but possible complication of stroke.
- ▶ Female sex and insular damage seem to be predisposing factors.
- ▶ Neurogenic-stunned myocardium may be a variant of takotsubo cardiomyopathy.
- ▶ Neurogenic-stunned myocardium has been associated with excessive catecholamines stimulation.
- ▶ In patients with severe cardiac dysfunction, high-dose insulin therapy may offer interesting inotropic and vasodilatory effects, while avoiding exogenous sympathetic stimulation.

Competing interests None.

Patient consent Obtained.

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