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Review

Aneurysmal subarachnoid hemorrhage as a trigger for Takotsubo syndrome: a comprehensive review

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Takotsubo syndrome (TTS) can result in acute heart failure and lead to a potentially life-threatening complication of aneurysmal subarachnoid hemorrhage (aSAH). The incidence of TTS in aSAH is less than 10% of all patients with aSAH, with a preponderance of postmenopausal women. Early indicators of TTS include elevated serum troponin levels and electrocardiographic abnormalities. The key finding is left ventricular wall motion abnormality. Echocardiography and coronary angiography help to establish the diagnosis. Vasopressors, milrinone, levosimendan, insulin, and anticoagulation may be required. The value of beta-blockers is a matter of controversy. TTS must not delay the treatment of a ruptured aneurysm. The clinical outcome in patients with aSAH and TTS is mostly determined by the aSAH and not the TTS.

Keywords

Subarachnoid hemorrhage; Intracranial aneurysm rupture; Broken heart syndrome; Myocardial stunning; Neurogenic stunned myocardium; Sympathetic disruption syndrome; Takotsubo syndrome

1. Introduction

In the New England Journal of Medicine in May 8th, 1986, a case study was published that reported a 44-year-old woman who presented to the hospital with retrosternal pain and pulmonary edema immediately after her son's suicide [1]. Acute cardiac symptoms induced by severe emotional stress have been previously described, but this case may represent the first description of Takotsubo syndrome (TTS). The term "Takotsubo cardiomyopathy" was coined by Hikaru Sato in 1990 [2]. The name "Takotsubo" refers to the shape of a Japanese octopus trap, which resembles the morphological appearance of the heart with abnormal contractility of the left ventricle. TTS is also known as "stress cardiomyopathy" or "broken heart syndrome", characterized by an acute and transient regional left ventricular systolic and diastolic dysfunction induced by severe emotional or physical stress. In 2018, Pelliccia proposed to replace the term "cardiomyopathy" in those patients with "syndrome" since several features of this disease (e.g., reversibility) do not fit with the concept of a cardiomyopathy [3].

In addition to emotional stress, severe brain damage is also described as a possible trigger. While ischemic stroke, cranial trauma, and intracerebral hemorrhage are less frequently encountered, aneurysmal subarachnoid hemorrhage (aSAH) is described as an immediate cause in up to 28% of the cases [4].

The appearance of a left ventricular wall motion abnormality with normal coronary arteries in patients with aSAH has been previously described [5–8]

The "*InterTAK Diagnostic Criteria*" for the diagnosis of TTS are as follows [the corresponding "*InterTAK Diagnostic Score*" (points)]:

– transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities or right ventricular involvement; the regional wall motion abnormality usually extends beyond a single epicardial vascular distribution. However, rare cases can exist where the regional wall motion abnormality is present in the myocardial territory of a single coronary artery (focal TTS)

– a trigger (emotional, physical, combined) can precede the TTS but is not obligatory [emotional trigger (24), physical trigger (13)]

– neurologic disorders (e.g., aSAH, stroke, seizures), as well as pheochromocytoma, may trigger TTS [psychiatric disorder (11), neurologic disorder (9)]

– new ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); rare cases exist without any ECG changes [absence of ST-segment depression (12), QTc prolongation (6)]

– levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common

– significant coronary artery disease may occur in TTS

– patients have no evidence of myocarditis

– postmenopausal women are predominantly affected [female gender (25)]

An updated diagnostic algorithm for patients presenting with chest pain and/or dyspnea has been proposed by Ghadri *et al.* [9–11]. The "*InterTAK Diagnostic Score*" allows differentiation between an acute coronary syndrome and TTS. A score of $>$70 points support the diagnosis of TTS.

In a subgroup of patients, a neurological disorder is the most likely cause of TTS. Kono *et al.* [12] in 1994 and Lee *et al.* [13] in 2006 coined the terms "neurogenic stunned myocardium" and "neurogenic stress cardiomyopathy".

The true incidence of TTS in association with aSAH is unknown. Published data suggest it occurs in 0.1–15% [14, 15], with other studies suggesting that this condition occurs less frequently [16, 17]. We encounter TTS in 4% of all aSAH patients, with a preponderance of women and a massive aSAH (Hunt and Hess IV and V). Due to the proximity of the medulla oblongata, which may play a critical role in the "brain-heart connection", it is conceivable that ruptured aneurysms in the posterior circulation are more prone to cause TTS than those in the anterior circulation [18, 19]. This is, however, not well supported by published data.

Several reviews on this subject have recently been published [20–22].

This review sought to provide an overview of TTS accompanying aSAH and propose a treatment strategy for this combined pathology.

2. Pathophysiology

Although the "connection" between the brain and heart in TTS development has been previously documented, the exact pathophysiological mechanisms have not yet been clarified.

Controversy exists in the pathophysiology of TTS after aSAH, as to the effects of an increased level of plasma catecholamines (Fig. 1). This has been shown in animal models [23] and clinical studies, with a preponderance of neurogenic norepinephrine (released from the cardiac sympathetic nerve fibers) over adrenal epinephrine (released by the adrenal gland) [24]. In line with this observation is the restoration of the cardiac function (e.g., the ejection fraction (EF)), which frequently occurs during the first week after an aSAH, accompanied by a normalization of the plasma catecholamine levels [25].

Greenhoot and Reichenbach [26], Zaroff *et al.* [27], and Y-Hassan [28] defined TTS as an acute cardiac sympathetic disease characterized by local cardiac norepinephrine seethe, followed by cardiac sympathetic nerve terminal eruption.

Goico *et al.* [29] proposed various hypotheses for the pathophysiology of TTS. During an initial phase, "stress" (localized in "cognitive brain centers") may activate a hypothalamic-pituitary-adrenal axis, resulting in an increased release of norepinephrine and epinephrine, contributing to a hyperactive sympathetic nervous system, and hyperresponsive myocardial tissue. The phenomenon of "stunned myocardium" is considered to be related to the catecholamine effect on cardiomyocytes. The stimulation of β1- and β2-adrenergic receptors are connected to the intracellular stimulatory G protein, the activation of the cyclic adenosine monophosphate (cAMP), and the protein kinase A. While epinephrine, through the β2-adrenergic receptor stimulation, has a positive inotropic effect at normal levels, it becomes a negative inotrope at abnormally increased levels via a coupling of the β2-adrenergic receptors to the intracellular inhibitory G protein. Norepinephrine has a positive inotropic effect through a β1-adrenergic receptor stimulation. The positive inotropic effect of norepinephrine-mediated β1-adrenergic receptor stimulation affects mainly the base of the left ventricle. The negative inotropic effect of excessive epinephrine-mediated β2-adrenergic receptor stimulation preferentially affects the left ventricular apex, leading to wall motion abnormalities. Microvascular dysfunction in TTS has been correlated with elevated levels of endothelin-1, plasminogen activator inhibitor-1 and von Willebrand factor.

In patients in the acute phase after aSAH, irrespective of cardiac issues, a massive sympathetic nervous activation with norepinephrine release has been reported [30]. Exogenous catecholamines are frequently required in aSAH patients during the acute phase to increase systolic arterial blood pressure to maintain cerebral perfusion. Intravenous administration of vasopressin [31], norepinephrine [32, 33], and dobutamine [34] have been described as potential TTS triggers. At pathological concentrations, catecholamines can cause β-receptor paradoxical negative inotropic effects [35]. Thus, this pathomechanism of TTS may result in cardiogenic shock.

Catecholamines act as strong vasoconstrictors of the cardiac microvasculature. Therefore myocardial stunning in TTS may be sympathetically induced and lead to microcirculatory dysfunction. The role of impaired coronary microcirculation has been discussed by several authors [36–38].

In "typical" TTS-patients, the left ventricular *apex* develops a wall motion abnormality. Mori *et al.* [39] found increased β-adrenergic receptor density and/or increased myocardial responsiveness to adenylate stimulation in apical myocardium in a canine model. Waller *et al.* [40] described a reverse TTS pattern with hypokinesis of the basal 2/3 of the left ventricle and a hypercontractile apex in a patient with aSAH. They suggest that variations in the density of adrenergic receptors may be responsible for this observation. Kumai *et al.* [41] compared 21 patients with typical and 10 patients

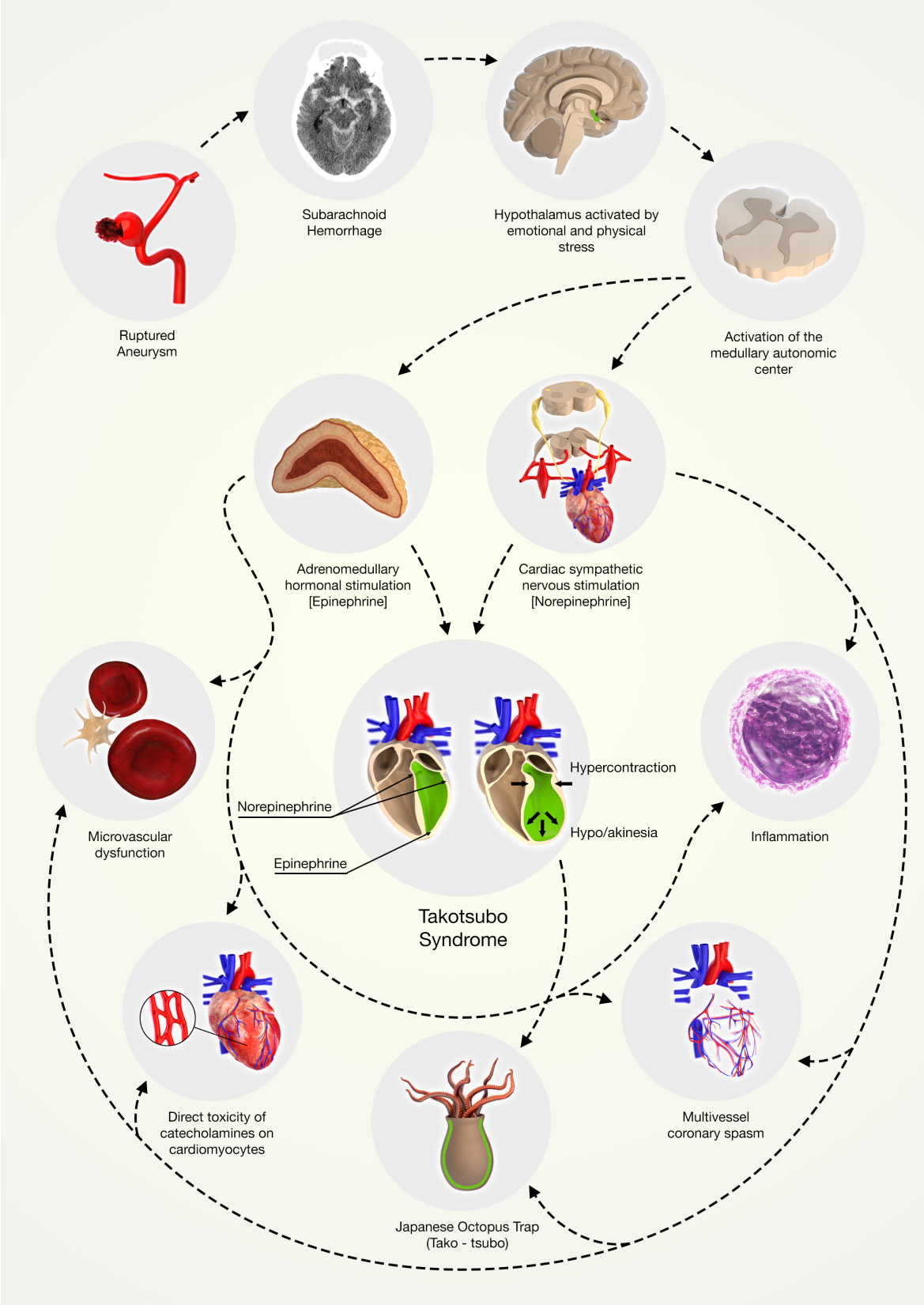

Fig. 1. Illustration of the potential pathomechanisms for aSAH-triggered TTS. The epinephrine pathway starts with adrenomedullary stimulation and is related to the apical ventricular hypokinesia. The norepinephrine pathway has the origin at the cardiac sympathetic nervous stimulation and is considered responsible for the basal ventricular hypercontraction.

with the reverse (basal) TTS, all related to aSAH. The patients with the reverse pattern were younger and showed higher plasma epinephrine levels. The management and prognosis, however, were essentially the same for both groups.

Ancona *et al.* [42] described the differences between neurogenic stunning in patients with aSAH (n = 14) and "classic" TTS (n = 22). They found a higher prevalence of women in both groups. Compared to patients with "classic" TTS, the patients with aSAH and neurogenic stunned myocardium were slightly younger (mean age 53 vs. 61 years), had no previous coronary heart disease, presented with heart failure (instead of chest pain), had no ST-segment elevation, had more T-wave inversion (64% vs. 27%), had less depressed left ventricle (LV) function, and presented less frequently with apical LV dysfunction (21% vs. 77%) and in >90% (vs. 45%) mid and basal LV dysfunction.

In both groups, an improved EF (mean 17%) at discharge was observed.

3. Diagnosis

The diagnosis and follow-up of TTS requires extensive laboratory, electrophysiological, imaging and circulatory examinations.

3.1 Chest radiography

Pulmonary edema with dyspnea can be the first sign of a developing TTS [18, 43, 44]. In neurogenic TTS, dyspnea (50%) is more frequent than chest pain (8%) [42].

3.2 Electrocardiography

In more than 95% of TTS patients, an abnormal ECG is found. The typical ECG findings include

– ST-segment elevations; they can be similar to that of an anterior (STEMI). ST-segment elevations in lead V1 and those limited to II, III, and aVF are findings in favor of an anterior STEMI

– inverted T waves; T-wave inversion is frequent and considered more prominent in TTS than in an acute coronary syndrome, QTc prolongation, and arrhythmias [21].

TTS rather than STEMI may be associated with anterior Q-waves and low voltage QRS. ST-segment depression suggests an acute coronary syndrome [11].

Not all patients with aSAH and ECG abnormalities develop TTS. Jung *et al.* [45] emphasized that ECG abnormalities after aSAH are more frequent (62%) than TTS (5% in this series). The ECG changes in patients with TTS typically last longer than the left ventricular dysfunction. Sinus bradycardia, atrioventricular block, atrial and ventricular fibrillation infrequently occur. Furthermore, in the acute phase of TTS, life-threatening ventricular arrhythmias can occur in up to 8% of cases [46].

3.3 Laboratory findings

The cardiac biomarkers usually found with TTS are also present in STEMI patients. The peak levels of creatine kinase myocardial band (CKMB) and high-sensitivity cardiac troponin T (hs-cTnT) are usually comparatively low in TTS [47, 48]. On admission, the ratio of the two markers, hs-cTnT and CKMB, is higher in TTS [49].

In TTS patients, an increase in the plasma concentration of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) is frequently observed days 1 and 2. The return to normal takes months [50].

The relatively moderate increase in troponin T (TnT) peak levels may discriminate TTS from an acute coronary syndrome. In a study by Fröhlich *et al.* [51], a cut-off level of the NT-proBNP (ng/L)/troponin T (μg/L) ratio of 2889 distinguished TTS from STEMI and an NT-proBNP (ng/L)/TnT (μg/L) ratio of 5000 distinguished TTS and NSTEMI. However, this ratio may be affected by when the measurements are made in the acute/subacute phase of TTS [51].

Compared with STEMI, left ventricular EF is more depressed in TTS patients, and the peak troponin level is lower. Nascimento *et al.* [52] observed EFs of 30% (TTS) versus 44% (STEMI) and peak troponin level of 7.6 ng/dL (TTS) versus 102 ng/dL (STEMI) (mean values). The product of troponin and EF (TEFP) with a cut-off at >250 predicts STEMI with high sensitivity and specificity [52].

Further insight into the diagnosis and treatment of TTS may come from advanced genetic analysis of microarray datasets [53]. None of these biomarkers, however, has so far replaced coronary angiography and echocardiography.

3.4 Echocardiography

Transthoracic echocardiography is the method of choice for detecting left ventricular dyskinesia in TTS. Apical ballooning is considered diagnostic, and mid-segments of the left ventricle, the septum, and the anterolateral wall can be involved. Abnormalities of the basal segments are less frequent and associated with aSAH and pheochromocytoma. Focal wall motion abnormalities of the anterolateral segments are rare [9, 21, 47].

Possible complications of TTS include hemodynamic compromise, mechanical outflow obstruction, pericardial effusion, intraventricular thrombus formation, and increased pulmonary artery pressure [54]. The distinction between apical ballooning and antero-apical stunning due to myocardial ischemia can be challenging, particularly in patients with multivessel coronary artery disease. Given the volatile nature of TTS, a systematic and comprehensive serial echocardiographic examination is recommended so that these complications can be promptly diagnosed [55]. In patients with aSAH and left ventricular systolic wall motion abnormalities, the apical function is preserved in about half of the cases [27].

3.5 Cardiac catheterization

Although echocardiography is the method of choice for diagnostic imaging in suspected TTS, coronary angiography and left ventricular angiograms play a significant role [54]. About 1–2% of all coronary angiographies lead to the diagnosis of TTS [56]. Angiography rules out coronary stenosis

and left ventriculography demonstrates the dyskinesia of the apical and hyperkinetic basal region. Desmet *et al.* [57] observed in 30% of patients with apical ballooning a small zone with preserved contractility in the most apical portion of the left ventricle ("apical nipple sign"), which was not observed in patients with STEMI.

In a recent review of 1016 TTS patients, 23% had concomitant obstructive coronary artery disease not related to the territory of the altered wall motion abnormality, and 41% had non-obstructive coronary artery disease [58].

Most patients with aSAH tolerate cerebral digital subtraction angiography (DSA) and can, if necessary, also be referred for coronary angiography. An elevated intracranial pressure (ICP) due to aSAH can result in severe cardiac and hemodynamic instability. Extended periods of supine positioning are frequently poorly tolerated and associated with an ICP increase. Thus, patients with aSAH are sometimes not ideal candidates for coronary angiography [42]. Coronary computed tomography is a viable alternative for hemodynamically unstable patients and those with elevated ICP with suspected TTS [59].

3.6 Myocardial biopsy

Myocardial biopsy is not part of the routine diagnostic work-up for patients with suspected TTS [60]. Several authors performed myocardial biopsies in TTS patients to obtain tissue for deoxyribonucleic acid microarrays [61, 62]. Biopsy findings of the cardiac muscle in patients with TTS show contraction-band necrosis and leukocyte infiltration and are considered a morphological correlate of a catecholamine-related injury [62, 63].

4. Treatment

Once the diagnosis of TTS is established, and the treatment is initiated, continuous monitoring of arterial blood pressure, heart rate, oxygen saturation, and central venous pressure is required. Frequent ECG, cardiac and pulmonary ultrasound examinations should be performed.

For patients with TTS and even more so for TTS triggered by aSAH, guidelines and comprehensive data from randomized trials are lacking. The current management of these patients is based on individual and institutional experience, retrospective literature analysis, and common sense. Madias recently published a comprehensive review of this subject [64].

The concurrent impact of a ruptured intracranial aneurysm (possibly with an elevated ICP), posthemorrhagic cerebral vasospasm, and TTS (possibly with heart failure) can create a therapeutic dilemma. The treatment of a ruptured aneurysm and an aSAH-triggered TTS will be discussed separately, knowing that the coordination of both therapeutic efforts is critical for success in clinical practice. Several drugs are available, together with the armamentarium of neurointensive care.

The following recommendations have found widespread acceptance [11].

– Patients with mild TTS without heart failure should be continuously monitored. Patients in the acute phase after aSAH require monitoring and treatment in an intensive care unit. Angiotensin-converting-enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), and β-blockers are potential options. Adrenaline, noradrenaline, dobutamine, milrinone, and isoproterenol should be avoided unless milrinone is needed to treat cerebral vasospasm.

– TTS-patients with heart failure and/or pulmonary edema may receive ACEI, ARB, and β-blockers. Diuretics and nitroglycerin are indicated as long as left ventricular outflow obstruction (LVOTO) is not present.

– For patients with hypotension or cardiogenic shock with primary pump failure, levosimendan, a left ventricular assist device (LVAD, such as Impella; intra-aortic balloon pump), and venoarterial extracorporeal membrane oxygenation (VA-ECMO) are considered. In the case of LVOTO fluid replacement, short-acting β-blockers and LVAD can be indicated, while diuretics, nitroglycerin, and an intra-arterial balloon pump should be avoided unless circulatory support is necessary.

– Arrhythmias may be treated with β-blockers and temporary pacing, while QT interval prolongation drugs and β-blockers in the case of bradycardia are contraindicated.

– Left ventricular thrombus and clinically apparent emboli are indications for anticoagulation with heparin, warfarin, or novel oral anticoagulants.

At least half of the patients with full-blown TTS require intubation, inotropic and vasopressor support, and anticoagulation [65]. In the rare case of ventricular fibrillation, immediate defibrillation is required [66]. The combination of TTS with posthemorrhagic cerebral vasospasm can be challenging. A detailed description of individual therapeutic regimens for neurogenic TTS can be found in the literature [67].

In patients presenting with *cardiogenic shock* due to TTS, an intraaortic balloon pump insertion for counterpulsation, an Impella heart pump, or extracorporeal life support (ECLS) may help overcome the hypotensive phase [43, 68]. The redirection of the blood flow towards the head can also be used to manage posthemorrhagic vasospasm [69]. Since these procedures require heparinization, a ruptured aneurysm must first be treated.

In a recent retrospective analysis, Napierkowski *et al.* [70] found no reduced mortality but higher costs in patients with cardiogenic shock from TTS treated with mechanical circulatory support [70].

In patients with aSAH and TTS, early treatment of the ruptured intracranial aneurysm should be attempted to prevent recurrent hemorrhage, especially if anticoagulation is required to treat the TTS. The cardiac wall motion abnormality can be associated with left intraventricular thrombus formation [71]. Apical TTS, thrombocytosis, and elevated plasma levels of C-reactive protein, d-dimers, and troponin are considered associated risk factors [72, 73]. A left ventricular thrombus carries the risk of an embolic large intracranial

vessel occlusion [74]. Anticoagulation with heparin or warfarin is the standard of care, which can only be initiated after the ruptured intracranial aneurysm has been excluded from the blood circulation [75].

Based on the individual circumstances, a variety of drugs should be considered. Many of these drugs can be administered intravenously (IV) or *per os* (PO). Those available as a PO variant only can be used (with some restrictions) via a nasogastric tube. Patients in the early phase after aSAH (also without TTS) frequently show a disturbance of gastrointestinal absorption. Therefore, for most patients suffering from aSAH and TTS, the IV administration of drugs is preferred.

4.1 β-blockers

The use of β-blockers in patients with aSAH and/or TTS is a matter of controversy. For patients with aSAH (without specified cardiac symptoms), Walter *et al.* [76] reported beneficial effects of β-blocker administration on clinical outcomes. In the International Takotsubo Registry with 1750 enrolled patients, the administration of β-blockers had no survival benefit [47]. However, beneficial effects of propranolol have been reported [77–79].

Madias listed the potential benefits of short- and ultrashort-acting β-blockers for TTS patients: protection from lingering autonomic sympathetic surge, relief of arterial hypertension and tachycardia, reduced myocardial oxygen demand, protection from atrial and ventricular arrhythmia, and reduction of left ventricular outflow tract obstruction [80].

In their series of 18 patients with aSAH and TTS, Talahma *et al.* [16] observed no benefit of administering β-blockers on clinical outcomes.

The standard dosages are

– 0.1 mg/kg/day propranolol IV, with a maximum of 4 mg
– 0.15–0.3 mg/kg/min esmolol IV for 24 h
– 10 mg/kg/min landiolol IV for 1–3 days

4.2 Angiotensin-converting-enzyme inhibitors

There are anecdotal reports concerning the clinical use of angiotensin-converting-enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) [81], but systematic studies are lacking. However, a meta-regression study reported that the likelihood of TTS recurrence in an ACEI/ARB-treated patient population was lower [82]. Templin *et al.* [47] demonstrated improved 1-year survival of TTS patients with ACEI/ARB treatment.

The standard dosage is 1.25–2.5 mg enalapril IV which can be tailored according to the clinical response.

4.3 Vasopressors

Norepinephrine has been used in patients with cardiogenic shock due to TTS in the initial stabilization phase [83].

The standard dosage is 0.1 μg/kg/min IV, and can be tailored according to individual response.

Dobutamine is used beyond the hyperacute resuscitation phase [83].

The standard initial dosage is 10 μg/kg/min dobutamine IV which can be tailored according to the response.

Since catecholamines trigger a TTS, the administration of vasopressors in these patients is unclear. Talahma *et al.* [16] reported good outcomes in 73% of the TTS patients who had received vasopressors. Naidech *et al.* [84] recommended dobutamine for aSAH patients with congestive heart failure with low systemic vascular resistance and arterial hypotension. In general, the management of TTS patients without the administration of catecholamines appears advantageous.

4.4 Milrinone

Milrinone is a non-catecholamine inotrope, which inhibits type III phosphodiesterase. Myocardial contraction is improved by enhanced calcium influx, with a limited effect on heart rate and cardiac oxygen consumption. Systemic vascular resistance is reduced, and arterial hypotension may occur, which may require additional norepinephrine infusion [85]. Naidech *et al.* [84] recommends milrinone for patients with normal systemic vascular resistance and normal systolic arterial blood pressure.

For the treatment of cerebral vasospasm after aSAH 8 mg milrinone diluted with physiologic saline solution to 50 cc is infused into the carotid artery for 30 min.

The cardiac dosage is an initial bolus of 50 μg/kg IV over 10 min, followed by a continuous infusion of 0.375 μg/kg/min).

4.5 Levosimendan

Levosimendan is a non-catecholamine inotrope, which neither increases the myocyte cAMP nor the cardiac oxygen consumption. It binds to the N-terminal pole of cardiac troponin C and stabilizes the calcium-bound conformation—a sustained interaction between the actin and myosin filaments during systole results in improved myocardial systolic function. Vasodilation is achieved via the opening of adenosine triphosphate-dependent potassium channels. Coronary perfusion is improved via a decrease in preload, pulmonary vascular resistance, and afterload. Good results in anecdotal cases have been published [67, 68, 86]. Experimental *in vivo* results and clinical experience have shown a potential therapeutic effect of levosimendan on posthemorrhagic cerebral vasospasm [87, 88], thus justifying the use of levosimendan in patients with TTS and cerebral vasospasm.

The standard dosage is a bolus with 12 μg/kg/min IV for 10 min followed by an infusion of 0.1 μg/kg/min for 24 h. However, in TTS patients with posthemorrhagic cerebral vasospasm, levosimendan might be given without a loading dose to avoid arterial hypotension resulting in a critical reduction of the cerebral perfusion pressure. Invasive hemodynamic and ECG monitoring is recommended for the treatment phase and the following 24 h to detect hypotension or cardiac arrhythmias [89].

4.6 Anticoagulation, antiplatelet therapy

Apical ballooning and elevated troponin levels are infrequently (2%) associated with left ventricular thrombus for-

mation and possibly subsequent thromboembolic complications in 0.8% of all TTS patients [90]. The long-term use of antiplatelet medication requires further investigation. In the International Takotsubo (InterTAK) Registry, treatment with aspirin upon hospital discharge did not affect short- or long-term prognosis [91]. Anticoagulation (IV or PO) should be considered in the case of left ventricular thrombus formation since early embolization remains a concern [73, 90]. Spontaneous resolution of a thrombus has also been observed [92].

The hemorrhage-related platelet activation must be considered in the setting of associated aSAH and TTS [93]. Platelet activation is a concern for the development of delayed cerebral ischemia and thrombosis of previously implanted intravascular stents. The value of point-of-care tests is a matter of controversy. For all patients, including those with aSAH, we perform Multiplate (Roche Diagnostic), and VerifyNow (Accriva) tests several hours after administering antiplatelet medication before any stent is implanted.

4.7 Insulin

Madias recently proposed TTS treatment according to the management principles for cardiac reperfusion injury after an acute myocardial infarction. Cardiac ischemic conditions are associated with a shift of the metabolism from fatty acid oxidation towards carbohydrate metabolism. Catecholamine-induced insulin resistance of the myocardium can be overcome by high-dosage insulin. The reasons to administer insulin in TTS are as follows [80].

Insulin

– increases the myocardial contractility, especially together with β-blockade and glucose infusion
– increases the cardiac output
– reduces the inotropic effect of norepinephrine
– at high dosage counteracts insulin resistance in patients with diabetes mellitus type 2
– increases the metabolic glucose uptake of the stunned myocardium.

Madias recommends

– to start with 30 g dextrose IV
– followed by a bolus 0.7–1.5 U insulin/kg
– followed by a continuous infusion of 1–1.45 U insulin /kg/h
– together with 30% dextrose infusion with potassium supplementation

An evaluation of the insulin/dextrose/potassium regimen in a clinical trial is pending. Vanderschuren *et al.* [94], however, published the case of a 52-year-old woman with TTS and cardiogenic shock after the rupture of an aneurysm of the anterior cerebral artery. She received the above-described combination of insulin (1.5 U/kg bolus and 1 U/kg/h infusion), 30% dextrose IV for euglycemia (80–120 mg glucose/dL) and potassium supplementation. A rapid cardiocirculatory improvement was achieved without the administration of catecholamines. On two occasions, an interruption of the insulin infusion was associated with a rapidly decreasing cardiac output [94].

Severe posthemorrhagic cerebral vasospasm has been observed in patients with aSAH and TTS [95]. Vasospasm is linked to delayed cerebral ischemia (DCI) following aSAH. Microthrombosis and microvascular dysfunction might be a common pathophysiological feature of DCI and TTS after aSAH [60, 96]. Similar therapeutic principles can be applied for both sequelae of aSAH.

Posthemorrhagic cerebral vasospasm makes patients vulnerable to even short periods of arterial hypotension. This must be kept in mind whenever low arterial blood pressure results from administering drugs like milrinone or levosimendan.

Craniotomy for the surgical clipping of a ruptured intracranial aneurysm may add "stress" to the "trauma" of the aneurysm rupture. Securing an aneurysm in the early phase (i.e., the first 2 days) after the rupture is the only way to prevent a recurrent hemorrhage but may coincide with the height of TTS. Data from clinical trials addressing this aspect are lacking. Patients with heart failure from TTS are not ideal candidates for surgical clipping; therefore early endovascular coil occlusion should be considered [95].

5. TTS and co-existent medical conditions

Epidemiological studies have shown that advanced diabetes mellitus with autonomic neuropathy may have a protective effect against the occurrence of TTS and may prevent TTS-related morbidity and recurrent TTS episodes [97].

TTS patients have a higher incidence of malignancies than the age-matched general population [60].

About 50% of TTS patients present with arterial hypertension, with an incidence of 27–83% [98]. Recurrence of TTS has been described in 4% of patients with a higher prevalence of arterial hypertension in these patients (87% vs. 68%) [99].

6. Prognosis and outcome

The prognosis of patients with aSAH and TTS is mainly determined by the underlying neurovascular disorder and cerebrovascular complications [18]. In the International Takotsubo Registry, the overall mortality was 5.6% per patient-year in the long-term follow-up, and the rate of serious adverse cardiac and cerebrovascular events was 9.9% per patient-year [47]. Thus, TTS *per se* is infrequently the main reason for fatal outcomes [65]. A coronary intervention in aSAH patients including heparinization and antiplatelet therapy without prior diagnosis and treatment of a ruptured aneurysm may result in a re-rupture of the aneurysm [43, 100].

Predictors for a poor neurological outcome are onset with cardiac arrest [101], right ventricular involvement, and the need for inotropic support [65]. In addition, elevated cardiac troponin after aSAH is associated with an increased risk of echocardiographic left ventricular dysfunction, delayed cere-

bral ischemia from vasospasm, and death or poor functional outcome at discharge [16, 84].

In the International Takotsubo Registry, 18% of the enrolled patients had *atypical* (i.e., non-apical wall motion abnormality) TTS, and those patients had an increased incidence of a neurologic disorder as the trigger. The in-hospital mortality with atypical TTS was 3.1% [9].

Talahma *et al.* [16] published a series of 800 patients with aSAH. The mortality in the entire series was 15%, while 4/18 patients (22%) with aSAH and TTS eventually died.

Norberg *et al.* [102] enrolled 455 SAH patients in their study. Elevated values of hs-cTnT, NTproBNP, and ST-T ECG abnormalities within 72 h after the clinical aSAH onset were associated with an increased risk of death during the first three months. TTS was associated with an increased risk of cerebrovascular events.

7. Conclusions

TTS occurs in 5–10% of all aSAH patients. Female gender, age $>$60 years, and a massive SAH are considered predisposing factors. The key finding is impaired wall movement of the left ventricle (frequently basal and not apical), confirmed on echocardiography. Medical treatment is individualized and may include vasopressors, β-blockers, levosimendan, and insulin/glucose infusion. The prognosis can be improved with treatments that addresses arterial hypotension, arrhythmias, and thromboembolic events. Early treatment of the underlying ruptured aneurysm is required to prevent recurrent aSAH and allows for systemic anticoagulation in the case of intraventricular thrombus formation.

Abbreviations

ACEI, Angiotensin-converting-enzyme inhibitors; ARB, angiotensin-receptor blockers; aSAH, aneurysmal subarachnoid hemorrhage; BNP, B-type natriuretic peptide; cAMP, cyclic adenosine monophosphate; CKMB, creatine kinase myocardial band; DSA, digital subtraction angiography; ECG, Electrocardiogram; ECLS, extracorporeal life support; EF, ejection fraction; hs-cTnT, high-sensitivity cardiac troponin T; ICP, intracranial pressure; InterTAK Registry, International Takotsubo Registry; IV, intravenous(ly); LV, left ventricle; LVAD, left ventricular assist device; LVOTO, left ventricular outflow obstruction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PO, per os; STEMI, ST-elevation myocardial infarction; TnT, troponin T; TTS, Takotsubo syndrome; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Author contributions

SW—selection of the relevant references, review of the pharmacological aspects; conducting the research process, specifically performing the evidence collection from the literature. TG—drafting of the work, management and coordination responsibility for the research activity planning and execution final approval, and agreement to the accuracy of the work, review of the cardiological aspects. PB—selection and analysis of the references, review of the neuroradiological aspects, verification, whether as a part of the activity, of the overall reproducibility of results and other research outputs. AC—managing the revisions of the manuscript, including reference integration, preparation, creation and presentation of the published work, specifically visualization, final approval, and agreeing to the accuracy of the work. OG—drafting of the work, reviewing the neurosurgical aspects, development of methodology, final approval, and agreeing to the accuracy of the work. HB—selection of the relevant references, conducting the research process, specifically performing the evidence collection from the literature; preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages, review of the neurological aspects, drafting of the work, final approval, and agreeing to the accuracy of the work. HH—primary drafting of the manuscript, selection, analysis of the references, revisions of the manuscript; Ideas; formulation or evolution of overarching research goals and aims, oversight and leadership responsibility for the research activity planning and execution, including mentorship to the core team.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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