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Takotsubo Cardiomyopathy as a Neurocardiogenic Injury after Subarachnoid Hemorrhage: Hemodynamics and Fluid Management

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Abstract

Takotsubo cardiomyopathy (TCM) is a life-threatening systemic disorder that may occur early after aneurysmal subarachnoid hemorrhage (SAH), but precise hemodynamics and fluid management remain unclear. Although TCM is often regarded as a reversible or self-limited phenomenon, it contributes significantly to morbidity and mortality of SAH patients, especially when it is complicated with other neurogenic injuries such as severe left ventricular dysfunction, pulmonary edema, and pneumonia. The purpose of this chapter is to introduce the current practice in intensive hemodynamic monitoring and goal-directed fluid management of post-SAH TCM using advanced hemodynamic devices based on our institutional protocol and the relevant literature and to evaluate their effects on clinical outcomes.

Keywords: Takotsubo cardiomyopathy, neurogenic stress cardiomyopathy, fluid therapy, pulmonary edema, subarachnoid hemorrhage

1. Introduction

Postoperative management of aneurysmal subarachnoid hemorrhage (SAH) is sometimes complicated by systemic cardiopulmonary complications to affect a significant impact on the morbidity and mortality of the patients [1, 2]. The neuro-cardiac injury of SAH is of particular importance because of their impact on the ability to manage blood pressure and volume status, especially in the setting of cerebral vasospasm or delayed cerebral ischemia (DCI). The pattern

of injury produced is commonly referred to as neurogenic stress cardiomyopathy [3]. One distinct morphological variant of stress cardiomyopathy is Takotsubo cardiomyopathy (TCM), which was first described by the Japanese physician in the early 1990s to be a reversible cardiomyopathy, the shape of which named after an octopus trap used by the native fishermen [4]. Although TCM is typically associated with acute emotional stress in postmenopausal women [5], triggers may also include physical stressors such as head trauma, intracranial bleeding, ischemic stroke, medical, and surgical procedures and catecholaminergic drugs [6]. Previous reports suggest the demographics and clinical characteristics of TCM are similar irrespective of their etiologies. However, there are notable differences in post-SAH TCM from other non-neurologic stressors in that the patients tended to be younger and more frequent in females than what is typically reported and had high in-hospital mortality (25%) [7].

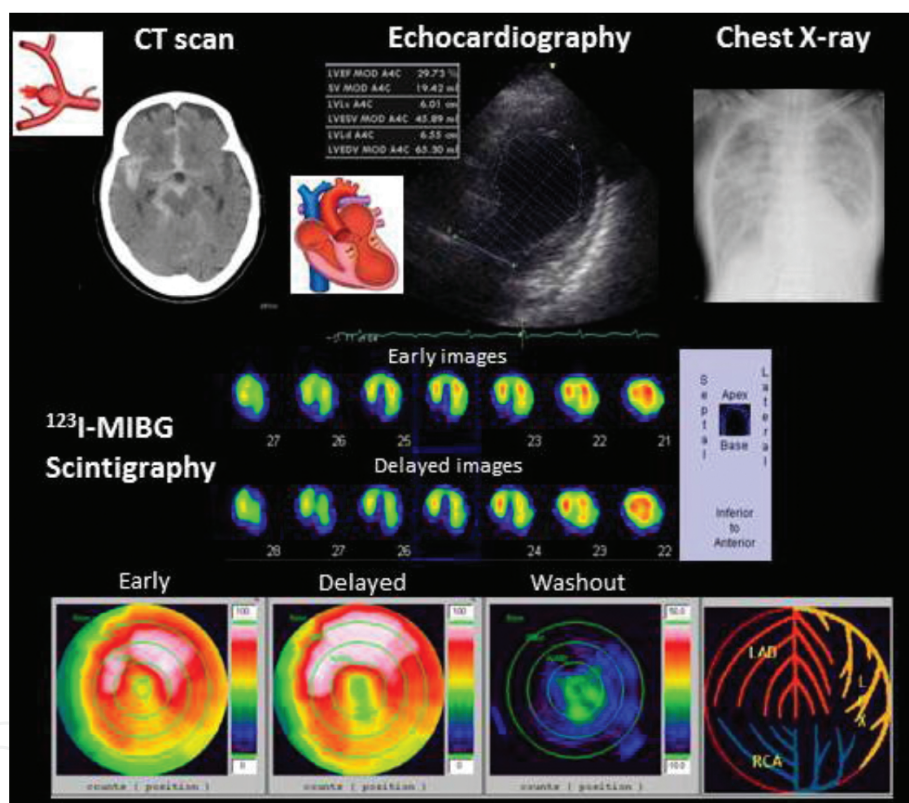


Figure 1. Subarachnoid hemorrhage-induced neurogenic injuries. Note that apical ballooning suggestive of Takotsubo cardiomyopathy (TCM) and left ventricular dysfunction detected by apical two-chamber view on initial echocardiogram. Acute pulmonary edema was also observed on chest X-ray. ^{123}I -metaiodobenzylguanidine (MIBG) SPECT depicting apical defect in the two-chamber view and the analysis of two-dimensional polar maps (bull's eyes) show decreased myocardial perfusion in apex. In 4-h delayed images, washout is increased, suggesting the presynaptic sympathetic dysfunction caused by TCM.

TCM is originally characterized by transient hypokinesia which results from apical wall motion abnormalities with sparing of the base. Although most of the TCM patients (>65%) can present such typical patterns on echocardiography (**Figure 1**), there are several different variants of regional wall motion abnormalities (RWMA) that spares the cardiac apex, as well as one that

affects the right ventricle. The right ventricle involvement is noted in 26% of the patients with TCM and bilateral pleural effusions are commonly seen in these patients [8].

The diagnosis of TCM is made based on a modified version of the Mayo Clinic Criteria [9] as described in **Table 1**.

1. Transient hypokinesis, akinesis or dyskinesis of the LV mid-segments with or without apical involvement; the RWMA extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present.
2. Absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture.
3. New ECG abnormalities (either ST elevation and/or T wave inversion) or modest elevation in cardiac troponin.
4. Absence of other precipitants such as pheochromocytoma and myocarditis.

LV: left ventricular; RWMA: regional wall motion abnormalities; ECG: electrocardiogram.

Table 1. The Mayo Clinic published diagnostic criteria for TCM after SAH.

Patients with akinesis or hypokinesis of left ventricular (LV) apical segments with preserved contractility of the basal segments are considered to have the apical variant of TCM (apical ballooning), while those with akinesis of the basal segments with preserved contractility of the apex and mid-ventricular segments are classified as having reverse TCM (non-apical ballooning).

A massive release of catecholamines into the systemic circulation after aneurysmal rupture has been considered responsible for SAH-induced TCM. In view of the literature reviews (**Table 1**), the incidence of TCM in SAH patients ranges from 0.8 to 17% [1, 2, 7, 10–12], which makes it a relatively common postoperative complication. However, the management of TCM becomes cumbersome in the setting of volumetric and hemodynamic therapy for DCI. In this chapter, we will review the current practice in intensive hemodynamic monitoring and goal-directed fluid management of post-SAH TCM using advanced hemodynamic devices based on our institutional protocol and the relevant literature and to evaluate their effects on clinical outcomes (**Table 2**).

	Total number	TCM [n (%)]	LVEF <40% [n (%)]	Mean age (years)	Female (%)	Poor grade (%)	DCI (%)	Poor outcome (%)
Mutoh et al. [12]	575	46 (8)	20 (43)	64	70	87	33	48
Talahma et al. [1]	800	18 (2.2)	N/A	63	78	33	N/A	44
Kilbourn et al. [2]	63	11 (17)	N/A	61	72	82	N/A	80
Inamasu et al. [10]	391	30 (7.7)	8 (27)	62	63	83	27	57
Abd et al. [7]	2276	19 (0.8)	14 (74)	45	100	58	N/A	N/A
Lee et al. [11]	661	8 (1.2)	4 (50)	56	100	88	38	N/A

Table 2. Incidence and characteristics of TCM in patients after subarachnoid hemorrhage.

2. Pathophysiology of post-SAH TCM

The underlying mechanism of TCM is not fully understood. Several theories have been proposed to explain its pathophysiology including excessive sympathetic stimulation, microvascular dysfunction, coronary artery vasospasm, and abnormal myocardial tissue metabolism [1]. An excessive release of catecholamines (catecholamine surge or sympathetic storming) immediately after insult associated with aneurysm rupture seems to have a pivotal role in the development of TCM. In fact, patients with TCM are at risk for fatal arrhythmias particularly those with SAH combined with intra-sylvian/intracerebral hematoma that involves the right insular cortex where sympathetic hyperactivation can occur [13, 14].

The deleterious effect of such brain–heart interactions may contribute to explain the observation that the outcome of patients with SAH can be predicted by measuring the levels of circulating catecholamine or myocardial sympathetic function. Using an isotope dilution technique, Naredi et al. [15] suggest that patients with subarachnoid hemorrhage exhibited a threefold increase in plasma norepinephrine within 48 h persisted throughout 7–10 days and normalized thereafter. Indeed, nuclear imaging using ^{123}I -meta-iodobenzylguanidine (MIBG), a radioactive marker allowing mapping of the autonomic nervous system of the heart also support the existence of sympathetic dysfunction (**Figure 1**) as a result of overactivation in the area of ventricular wall dysfunction with preserved coronary blood flow [16].

Histopathological findings support this theory since patients presented with typical TCM showed extensive area of myocardial thinning and myocyte edema at the cardiac apex in which degenerative myocardium with histiocyte and lymphocyte infiltration, and contracture-like necrotic bands, but a less severe pathology at the base [17, 18]. Oxidative stress can lead to myocardial necrosis, remodelling, and contractility disturbances [8]. Neuropathological evidence of Lewy body-like cytoplasmic inclusions in both dorsal nuclei of the vagus nerve suggests that disorders of the parasympathetic nervous system may also be associated with a consequence of TCM [17].

On the other hand, the predominance of TCM in female subjects implicates possible properties of genetic predisposition and/or estrogen deficiency [8]. Goodloe et al. [19] investigated functional adrenergic polymorphisms in 28 TCM patients to suggest that TCM was enriched for variants within functional domains, although the polymorphism frequencies were similar to population controls as described previously. Kuo et al. [20] presented a case series of 18 TCM patients and concluded that the lack of estrogen replacement in the postmenopausal state may predispose women to Takotsubo cardiomyopathy. Based on the results from TCM in a mother–sister pair, it has been suggested that the segregating rare variants in four genes (ADH5, CACNG1, EPHA4, and PRKCA) [19] may synergistically confer myocardial vulnerability and risk for TCM in the setting of a postmenopausal hormonal environment and a catecholamine trigger.

The available literature provides no clear answer about the safety of general anesthesia in SAH patients complicated with TCM, and whether the treatment of the aneurysms should be surgical or endovascular. However, it appears that TCM may not be a contraindication to

surgical obliteration of the aneurysms as long as the patient is hemodynamically stable [10], while multiple other reports showed that endovascular intervention is the preferred modality of treatment in these patients [21]. In fact, 37–61% of patients underwent surgical clipping for their aneurysms which elucidate the safety of anesthesia for microsurgical clipping even in the setting of TCM [1, 10, 12]. Furthermore, neither clipped nor coiled patients developed serious perioperative cardiopulmonary complications, although relatively higher incidence of fatal procedure-related complications was demonstrated in patients underwent coiling [10].

3. Hemodynamics of TCM after SAH

The hemodynamic changes of TCM that occur during the course of SAH are not fully understood, presumably because of the complicated underlying acute pathophysiological mechanisms that could merely be an innocent finding reflecting the general population.

Although the RWMA associated with TCM is transient with resolution generally within several days to weeks [22, 23], it contributes significantly to cardiopulmonary hemodynamics following SAH, especially when it is combined with other neurogenic injuries such as pulmonary edema, cardiogenic shock, and life-threatening arrhythmia [24, 25]. The RWMA diagnosed on echocardiography have been reported in up to 20% of patients after SAH [2], which is sometimes extensive enough to reduce left ventricular ejection fraction (LVEF). Therefore, in addition to pulmonary edema and hypoxia, TCM may lead to low cardiac output (CO) and hypotension to reduce cerebral perfusion pressure. The incidence of SAH-induced LV dysfunction has been estimated at around 5–10% [26], the development of which following TCM can increase the risk of DCI [11, 27] and poor outcome [12]. Moreover, TCM is associated with a 25% incidence of left ventricular outflow tract (LVOT) obstruction [28], and thus we have to be carefully monitor the cardiac functions to avoid increased intraventricular pressure gradient particularly when treating the related cardiogenic shock or post-SAH DCI.

4. Intensive fluid management for post-SAH TCM

4.1. Hemodynamic monitoring

Cardiovascular monitoring is essential for the diagnostic and therapeutic management of critically ill patients. Of particular, early hemodynamic assessment is importance for adequate cerebral circulation in patients with SAH. Echocardiography is currently the most frequently used noninvasive imaging modality for bedside assessment of LV function [29–31], but is not ideal for real-time monitoring of systolic function because of its high intra- and inter-observer variability [32].

Hemodynamic monitoring is essential for the diagnosis and therapeutic management of critically ill patients. Several different methods and techniques are used to monitor patients

with cardiopulmonary complications, although none are ideal (i.e., noninvasive, safe, reproducible, assessing both preload and lung edema volumes, as well as cardiac function) [33]. Unfortunately, the use of such monitoring devices has been limited in neurocritical care, presumably due to inexperience and complexity of handling multiple hemodynamic parameters (e.g., pulmonary artery catheter) [34]. Recently, several studies examined acute hemodynamic changes following SAH using an advanced bedside transpulmonary thermodilution (TPTD) device [12, 35–38].

The single-indicator TPTD method incorporated into the PiCCO/PulsioFlex (Pulsion Medical Systems, Munich, Germany) or EV-1000 (Edwards Lifesciences, Irvine, CA, USA) system measures the change in temperature over time at a thermistor-tipped peripheral arterial catheter inserted into the femoral or brachial artery by triplicate injections of 15-mL boluses of ice-cold saline via the central venous line [39]. The TPTD algorithm calculates CO by analysis of the thermodilution curve using the Stewart–Hamilton equations, which are less-invasive but comparable with those by the established PAC technique [40].

The accuracy of continuous CO measurements, superiority of the TPTD-derived volumetric parameters for estimating cardiac preload (based on global end-diastolic volume (GEDV)) compared with measurement using fluid balance, central venous pressure or a pulmonary artery catheter [41], and the utility of EVLW to discriminate pulmonary edema [37, 42] have been validated in clinical studies in SAH. These hemodynamic data can provide to analyze the cardiac function index (CFI, normal value: 4.5–6.5 per minute), which is the ratio of CO to GEDV [39]. Previous data suggest that CFI is closely related to the LV fractional area of change measured by echocardiography [43] and that CFI can be used to accurately assess the effects of positive inotropic therapy with dobutamine in acute circulatory failure [29].

4.2. Hemodynamic parameters for monitoring TCM

We have recently demonstrated that CFI measured by TPTD provides reliable real-time estimation of LV systolic function in 46 patients with TCM [12]. This study has an advantage of including the *largest* reported number of patients with post-SAH TCM who were successfully monitored for cardiac performance and volume status for approximately 14 days. CFI behaves like an index of LV systolic function because (1) it is fairly well correlated with the echocardiographic LVEF and reliably tracks treatment-induced changes in LVEF, and (2) it is not affected by fluid loading, but increased after administration of an inotropic agent. The decrease in CFI of <4.0 per minute is valuable for detecting LV dysfunction in TCM defined by LVEF <40% (sensitivity of 82% and specificity of 84%), which is the point at which inotropic support should be considered.

At initial measurement on day 0 during the first 24 h after SAH, depression of LV systolic function (CFI 3.3 per minute) mainly attributable to low CO (2.2 L/min/m²) was observed for patients with TCM. Hypovolemia defined by decreased GEDV (635 mL/m²) was notable in patients with LV dysfunction (LVEF <40%). In our population, we could not detect any significant difference in HR, MAP, CVP, or SVRI between the groups with and without LV dysfunction throughout the acute period of 2 weeks after SAH. It has also been suggested that TCM combined with LV dysfunction has a longer duration of low CFI

(<4.0 per minute, corresponding to predicted LVEF <40% [29]) with a mean difference of 4 days and more frequencies of pulmonary edema defined by EVLW > 14 mL/kg after day 4 (55%) (Figure 2).

4.3. Choice of drugs for post-SAH TCM patients

Medical treatment of arterial vasospasm following aneurysmal subarachnoid hemorrhage (SAH) generally consists of triple H (hypertensive-hypervolemia-hemodilution) therapy [44, 45] or its modification [46–48], which frequently relies on inotropic agents in order to increase CO. Although the optimal treatment is still a matter of debate, given the relationship between catecholamine hypersecretion and subsequent development of TCM, intensivists are often

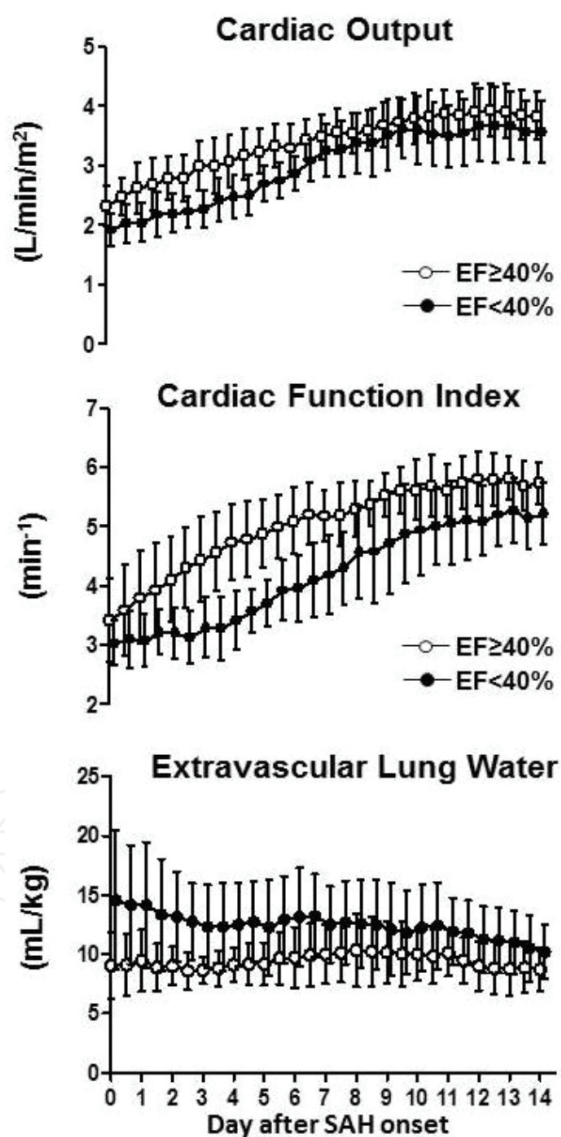


Figure 2. Changes in hemodynamic parameters over 2 weeks in 30 patients with Takotsubo cardiomyopathy following subarachnoid hemorrhage. Note that cardiac function index more clearly traces changes in cardiac function than cardiac output particularly in patients with left ventricular dysfunction [ejection fraction (EF) < 40%]. Increased extravascular lung water in this subgroup can also be detected. Modified with permission from Ref. [12].

reluctant to use inotropes and vasopressors even in patients who may benefit from cardiogenic shock or hemodynamic therapy for DCI. Although there is general agreement in the literature about avoiding vasopressors in TCM patients because of the adverse effects on catecholamine hypersensitivity, the recent data suggest that vasopressors may be used safely by careful monitoring of the hemodynamic parameters [1, 49]. In fact, most patients (61%) had already been administered vasopressors prior to the diagnosis of TCM, in which more than 60% remained on the same treatment and most of them (86%) had good outcome [1]. There is only a case of TCM reported as a direct effect of catecholamine stimulation, including an anecdotal case of de novo TCM in a patient treated with dobutamine for symptomatic SAH vasospasm [50]. In select patients, the use of intra-aortic balloon pump (IABP) may be beneficial as an adjunctive therapy of patients with comorbid DCI and TCM who become intolerant to aggressive pharmacologic hemodynamic augmentation [51].

Milrinone could be a good alternative when inotropes are required in TCM and when dobutamine infusion is associated with tachycardia [52]. The use of milrinone has been proposed to augment the cerebral perfusion in TCM giving its combined inotropic and vasodilating properties [53]. Milrinone is a phosphodiesterase-III inhibitor that increases calcium influx in the myocardium which leads to increased cardiac contractility without β -agonist action, resulting in less tachycardia [52] and myocardial oxygen consumption [54]. However, milrinone may induce hypotension as a result of peripheral vasodilatory property, which may require intensive hemodynamic monitoring during the management.

In the case of concurrent LVOT obstruction associated with post-SAH TCM that may have a paradoxical decrease in CO following administration of inotropic pressors, discontinuation of the inotropes and maintenance of hypervolemia may be required in order to optimize cerebral perfusion and prevent ischemia [27]. If a patient with TCM is deteriorating and has a low CO with LVOT, cardiogenic shock, and progressive multiorgan failure, temporary LV assist devices (LVAD) or extracorporeal membrane oxygenation (ECMO) as a bridge-to-recovery may be useful, as there is a possibility that the ventricular function will recover fully [55].

The role of β -blockers in SAH patients with TCM remains unclear. Patients who had been treated with β -blockers prior to the SAH were associated with a lower risk of developing TCM [56]. In one small study (n = 18), the use of β -blockers prior to or after the diagnosis of TCM was not associated with a significant difference in neurological outcome [1]. The role of a newer inotropic agent levosimendan is more controversial, with mixed expert opinion based on preclinical and limited clinical experience [1, 55]. Future studies on the effectiveness of these drugs in prevention or treatment of TCM may be warranted in larger population.

4.4. TPTD-guided early goal-directed fluid management

Fluid management of peri- and postoperative SAH patients is aimed primarily at maintaining CO to increase cerebral blood flow, and at preventing hypovolemia by minimizing cardiopulmonary complications [44, 57, 58]. The practical usefulness of early goal-directed fluid therapy (EGDT) with TPTD has been proposed in SAH patients including those suffered from TCM [12, 36, 37, 41, 42, 59].

Hemodynamic stability is defined as CO ≥ 3 L/min/m², GEDV ≥ 680 mL/m², and ELWI ≤ 14 mL/kg (the upper limits chosen were the values associated with a higher risk of mortality in patients with pulmonary edema) [60]. If CO fell below the target value due to hypovolemia, patients received 500 mL of either crystalloid fluid or 6% hydroxyethyl starch. If this fluid loading did not increase the GEDV to above the target value, and the low CO persisted for at least 8 h, 25% albumin solution was administered. If the low CO persisted even with hypervolemia (GEDV ≥ 850 mL/m²) and fluid therapy for at least 12 h, inotropic support was initiated with dobutamine [61] or milrinone [12, 37] to maintain CO above the target value. If the patient had elevated EVLW (>14 mL/kg) and any signs of congestive heart failure or pulmonary edema (such as bilateral pulmonary infiltrates or cardiomegaly with a cardiothoracic ratio $>50\%$ on chest radiography), furosemide (5 mg bolus) was administered intravenously.

According to our institutional protocol, clinical deterioration due to DCI or evidence of cerebral vasospasm on transcranial Doppler ultrasonography (mean flow velocity in the middle cerebral artery >120 cm/s) was treated with hyperdynamic therapy with incremental doses of dobutamine (3 μ g/kg/min, maximum 15 μ g/kg/min) or milrinone (0.125 μ g/kg/min, maximum 0.75 μ g/kg/min) to raise the CO above the normal limit (>5.0 L/min/m²) or to resolve the deficit [12, 62, 63]. Recovery of RWMA [64] and the absence of LVOT obstruction were confirmed by echocardiography before the initiation of hyperdynamic therapy to avoid adverse effects due to the use of inotropic agents [27].

4.5. Outcome of EGDT in post-SAH TCM

In TCM patients managed with aforementioned post-SAH EGDT, multivariate logistic regression analysis showed that persisted low CFI (<4.0 per minute) for ≥ 4 days was independently associated with DCI (odds ratio, 1.87) and poor functional outcome at 3 months (modified Rankin Scale of 4–6: odds ratio, 1.92). In addition, coexisting pulmonary edema (EVLW > 12 mL/kg) also increased the risk of poor functional outcome at 3 months (odds ratio, 1.85). The results may have an advantage of EGDT because neither a lower LEVF nor the presence of concomitant pulmonary edema correlated with unfavorable outcomes in 30 SAH patients with TCM managed by conventional fluid management using echocardiography and standard hemodynamic parameters [10]. Furthermore, the finding that EGDT has a lower incidence of therapy-related pulmonary edema than standard care [65] may support the value of intensive hemodynamic monitoring.

5. Conclusion

TCM is a well-recognized neurogenic stress-induced complication early after SAH. It is a self-limiting condition but often adds an additional layer of clinical morbidity to a patient particularly suffering from DCI. Our clinical data suggest that prolonged cardiac dysfunction and concurrent pulmonary edema can increase the risk of DCI, contributing to poor functional outcome in patients with SAH complicated with TCM. Serial measurements of CFI and EVLW

may provide an easy bedside method of estimating changes in LVEF in TCM and predicting the outcome, as well as detecting fluid therapy-related cardiopulmonary complications.

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