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CASE REPORT

Tissue Plasminogen Activator in Acute Cardiac Arrest

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Abstract

Tissue plasminogen activator (TPA) is indicated as an empiric therapy for refractory out-of-the-hospital cardiac arrest for suspected pulmonary embolism and myocardial infarction. Intracranial hemorrhage following TPA administration is a rare complication resulting in increased morbidity and mortality. A history of intracranial bleed, oral anticoagulant use prior to hospital admission, low body weight, and unstable hypertension with blood pressure above 180/110 mmHg at the time of presentation are associated with intracranial bleeding following tPA administration. Dedicated imaging including a Computed Tomography of the head without contrast, while feasible for patients presenting with acute stroke, is impractical in the setting of cardiac arrest. Here we report a case of 66 years old patient who presented in context of refractory cardiac arrest with recurrent PEAs with interval return of spontaneous circulation (ROSC) and was given tPA with eventual ROSC. He was subsequently found to have both a subarachnoid and intraventricular hemorrhage.

Keywords: Cardiac arrest, Tissue plasminogen activator (TPA), Intracranial hemorrhage, Oral anticoagulant, Myocardial infarction, Pulmonary embolism

1. Introduction

Cardiac arrest is defined by the American Heart Association as a sudden onset collapse, followed by loss of consciousness and absence of both spontaneous respiration and pulse requiring CPR.[1–3] The estimated overall incidence of sudden cardiac death after myocardial infarction (MI) ranges from 2 % to 4 % per year,[4–7] with a 10-fold increased rate of deaths within the first 30 days of MI.[7] Massive pulmonary embolism can lead to cardiac arrest in 41 % of patients,[1,2] with most patients presenting in the context of asystole or pulseless electrical activity (PEA).[1,8–10] Intriguingly, 4–10 % of all out-of- hospital cardiac arrests are due to subarachnoid hemorrhage; however, the pathophysiological mechanism remains unclear.[11–14]

Asystole and pulseless electric activity are the two most common presentations of cardiac arrest secondary to massive pulmonary embolism.[1] Several studies have affirmed emergent administration of aggressive thrombolytic therapy, such as TPA, along with ongoing cardiopulmonary resuscitation as a reasonable and empiric approach in cases of cardiac arrest secondary to suspected fulminant pulmonary embolism.[1] Intracranial hemorrhage as a complication of thrombolysis is rare but may give rise to fatal complications.[15] Risk factors for intracranial hemorrhage should be assessed prior to initiating thrombolytic therapy. Identifying patient-specific risk factors such as advanced age, chronic hypertension, hyperglycemia, low body mass index, history of congestive heart failure, low platelet count, and previous stroke can serve as a valuable guide in the decision to initiate thrombolytic therapy or consider alternative treatment options.[15–17]

2. Case presentation

EMS was activated for a 66-year-old male who was found unresponsive by his wife in the bathroom. Five minutes before he was found unresponsive, he complained of a severe headache. Medical history was notable for hypertension, coronary artery disease, left lower extremity deep vein thrombosis, and aneurysmal subarachnoid hemorrhage with left-sided residual neurologic deficits.

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Home medications included aspirin 81 mg daily, lisinopril 40 mg daily, metoprolol succinate 50 mg daily, and pravastatin 40 mg daily.

Upon EMS arrival, the patient was unresponsive with bilateral pinpoint pupils and bluish discoloration of lips, hands, and feet. He was noted to have a Glasgow coma scale (GCS) of 3 and a pulse of 88 beats per minute. During transport to the emergency department, he became pulseless and CPR was initiated. Three rounds of epinephrine were administered in route to the emergency department. On arrival to the emergency department, he continued to be in pulseless electrical activity with associated cyanosis. Vital signs were remarkable for heart rate of 0 beats per minute and body temperature of 36.8 °C.The patient's pupils were 3 mm fixed, gaze fixed midline with negative oculocephalic, corneal and gag reflex. There was no response to noxious stimuli. Stat laboratory diagnostics demonstrated an elevated lactic acid (13.6 mmol/L; reference range 0.5–2.2 mmol/L) and troponin that eventually peaked at 14,671 ng/L (Table 1). The patient was emergently intubated and CPR was continued; return of spontaneous circulation (ROSC) was achieved 45 min later. His electrocardiogram post ROSC showed atrial fibrillation at 74 bpm with diffuse ST segment depressions in the anterolateral leads consistent with cardiac ischemia (Fig. 1).

Unfortunately, within 5 min of achieving ROSC, the patient suffered another episode of PEA arrest. Due to recurrent PEA arrests, TPA 50 mg was administered for presumed myocardial infarction and/or pulmonary embolism. ROSC was obtained in 3 min. Upon stabilization, diagnostic imaging included a Computed Tomography (CT) of the chest/abdomen/pelvis that did not show evidence of pulmonary embolism; however, significant findings included findings characteristic of pulmonary artery hypertension, a 2.6 cm ascending thoracic aortic aneurysm, and coronary calcifications. EKG showed normal sinus rhythm with ongoing ST segment depressions in the anterolateral leads and resolution of the anterolateral T wave inversions. CT of the head without contrast demonstrated a high-grade subarachnoid hemorrhage and intraventricular hemorrhage with hydrocephalus (Fig. 2A and B). Echocardiogram demonstrated a preserved left ventricular ejection fraction without evidence of regional wall motion abnormalities or intracardiac thrombus. The patient's family was unable to provide a complete history given the emergency nature of the event hence why chart review was performed later. Further chart review revealed that his medical history was also notable for subarachnoid hemorrhage due to a posterior inferior cerebellar artery (PICA) aneurysm rupture 4 years ago. The aneurysm had never been secured because of anatomic difficulties. That hospital course was further complicated by vasospasm with delayed cerebral ischemia and right middle cerebral artery stroke.

Due to the presence of intracranial hemorrhage post-ROSC, tPA-coagulopathy was treated with 10 units of intravenous cryoprecipitate. The patient

Table 1. Laboratory result.

Labs		Normal range	Result
Sodium		136–145 mmol/L	137 mmol/L
Potassium		3.4–4.5 mmol/L	4.3 mmol/L
Chloride		98–107 mmol/L	102 mmol/L
Blood urea nitrogen		20–31 mg/dL	22 mg/dL
Creatinine		0.6–1.1 mg/dL	1.0 mg/dL
Calcium level		8.7–10.4 mg/dL	9 mg/dL
AGAP		5–15 mg/dL	10 mg/dL
AST		0–33 units/L	40 units/L
ALT		10–49 units/L	38 units/L
Alkaline phosphatase		46–118 units/L	72 units/L
Total Bilirubin		0.2–1.1 mg/dL	1 mg/dL
Random blood glucose		65–140 mg/dL	138 mg/dL
Troponin ng/L		0–53	14,671
Lactic acid mmol/l		0.5–2.2	13.6
PT seconds		11.8–14.6	18.7
INR		0.8–1.2	1.6
ABG	PH arterial	7.35–7.45	7.34
	PCO2 arterial	35.0–45.0 mm Hg	42 mm Hg
	PO2 arterial	83–108.0 mm Hg	82 mm Hg
	HCO3	21–28 mmol/L	22.7 mmol/L
	O2 saturation arterial	95–100 %	97.5 %

AGAP: Anion gap, AST: Aspartate aminotransferase, ALT: Alanine transaminase, INR: International normalized ratio, ABG: arterial blood gas.

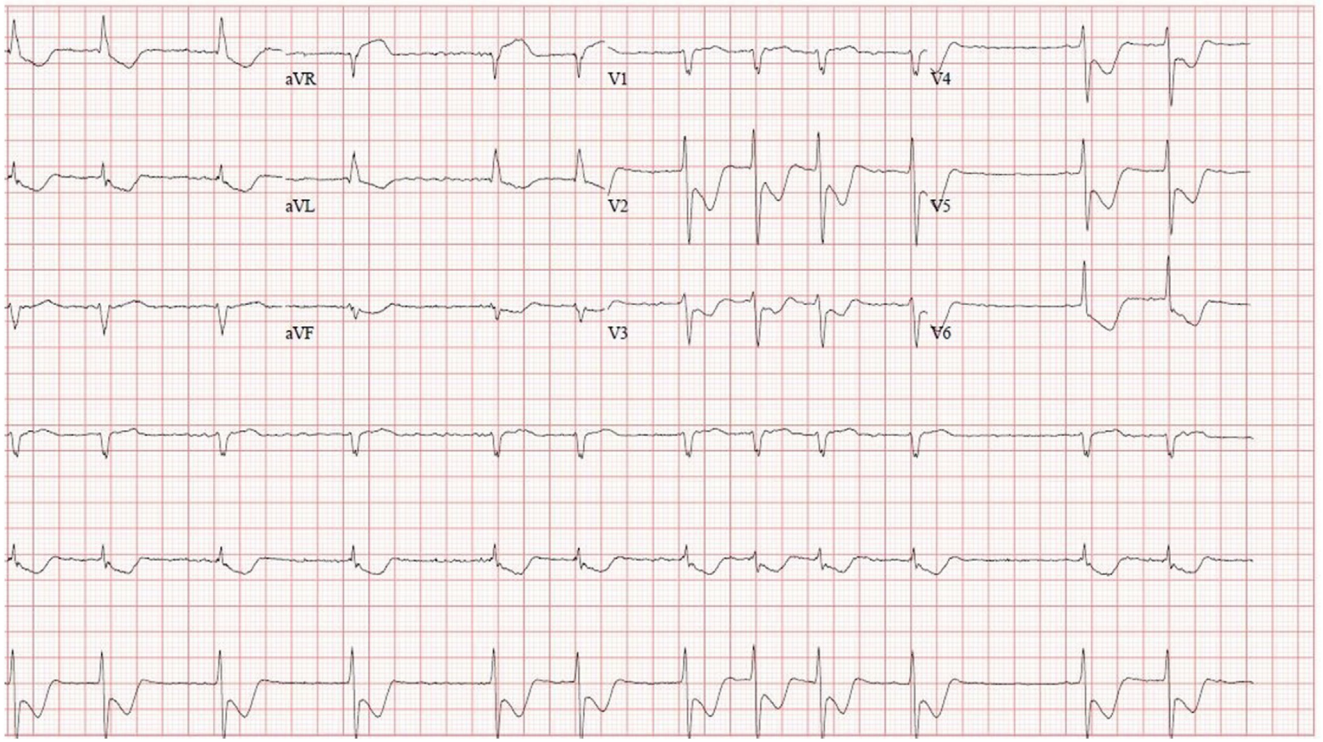

Fig. 1. Electrocardiogram demonstrating atrial fibrillation with diffuse ST segment depressions in the anterolateral leads.

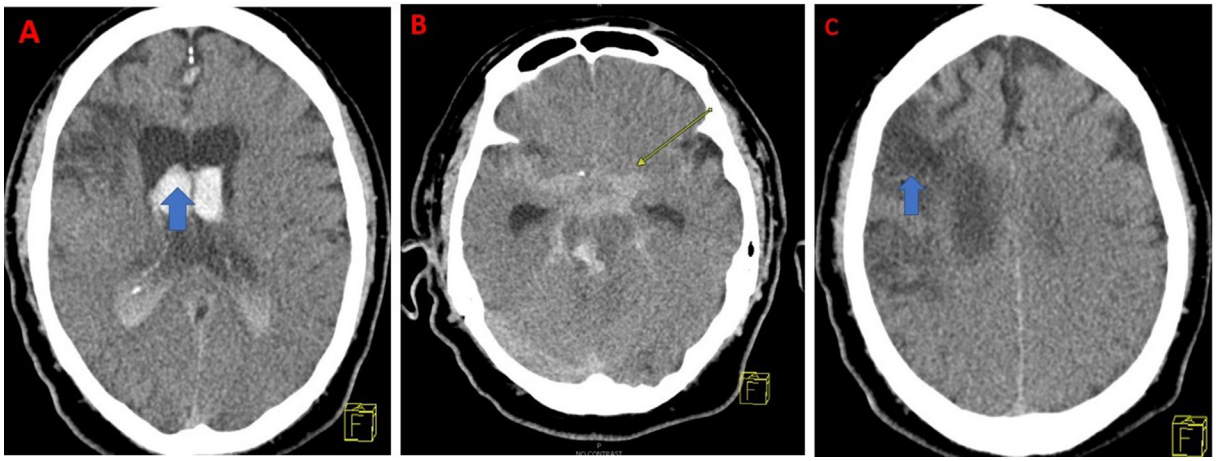

Fig. 2. Computerized tomography imaging of head without contrast (A)Demonstrates: high-grade subarachnoid hemorrhage (arrowhead) (B)Demonstrates: cisternal subarachnoid hemorrhage at the level of circle of Willis leading to intraventricular hemorrhage with hydrocephalus (arrowhead) (C)Demonstrates: loss of grey-white matter differentiation, a hallmark of anoxic brain injury (arrowhead).

was initiated on levetiracetam for seizure prophylaxis. The hospital course was complicated by undifferentiated shock requiring vasopressor support. The discussion between the neurology and neurosurgery teams revealed an irreversible anoxic brain injury for which compassionate extubation was performed (Fig. 2C).

3. Discussion

Cardiac arrest is the abrupt cessation of cardiac activity compromising the perfusion of tissues. A primary cardiac etiology has been reported in 65 %–89 % of the patients who suffer from out-of-hospital cardiac arrest (Table 2),[18,19] yet the etiology may be unclear, particularly in patients with comorbid medical/psychiatric conditions.[1] About 80–90 % of patients who develop cardiac arrest due to a cardiac etiology were found to have ventricular fibrillation at the time of collapse.[20–22]

Intracranial hemorrhage is a noncardiac cause of sudden cardiac arrest. The pathophysiology of cardiac arrest in the context of intracranial hemorrhage may be explained by a tremendous catecholamine surge leading to cardiac stunning. In addition, the abrupt elevation of intracranial pressure from the hemorrhage results in brainstem dysfunction causing respiratory arrest and hypoxia, which in turn precipitates the release of adenosine that hinders cardiac contractility and atrioventricular conduction.[23] Death due to subarachnoid hemorrhage (SAH) is often sudden, as compared to that of ischemic stroke and other types of intracranial hemorrhage.[24–26] Mitsuma et al. profiled 244 patients who presented to the emergency department with out-of-hospital cardiac arrest and found that

Table 2. Causes of sudden cardiac arrest[37–40].

Cardiac causes	• Ischemic heart disease: myocardial infarction, coronary spasm, anomalous coronary origin • Cardiomyopathies: alcoholic, idiopathic, hypertrophic, fibrotic, myocarditis, arrhythmogenic right ventricular cardiomyopathy, obesity related • Inherited channelopathies: long QT syndrome, short QT syndrome, Brugada syndrome, early repolarization syndrome, catecholaminergic polymorphic ventricular tachycardia • Valvular disease: aortic stenosis • Congenital heart disease: Tetralogy of Fallot
Noncardiac causes	• Pulmonary embolism • Intoxication/Overdose • Trauma • Major bleeding (Gastrointestinal bleeding, aortic rupture, intracranial hemorrhage) • Hypovolemic shock • Near drowning

the frequency of SAH was noted to be approximately 6 %; ROSC was obtained in only 15 % of patients. However, all the resuscitated patients later passed away due to PEA or asystole.[14] In our case, the possibility of SAH causing cardiac arrest cannot be excluded. Our patient reported a severe headache within 5 min of being found unresponsive along with a discovered history of unsecured posterior inferior cerebellar artery (PICA) aneurysm.

About 90 % of sudden cardiac arrests associated with fulminant pulmonary embolism occur within a period of 1–2 h of the initial symptoms, such as chest discomfort, dyspnea and syncope.[27] Due to obstruction of the pulmonary artery, vasoconstrictor mediators are released from thrombi that cause increased right ventricular afterload. This results in increased right atrial pressure along with decreased left ventricular end-diastolic filling, ultimately leading to cardiogenic shock.[28] There is a lack of uniformity in the initial approach to cardiac arrest secondary to fulminant pulmonary embolism. Some studies have concluded that emergent thrombolysis or surgical embolectomy performed even in ongoing CPR reduces the overall mortality rate,[1,29–37] while Yousuf et al. demonstrated no statistically significant difference in survival to discharge or in ROSC observed following TPA compared to those treated with standard therapy.[1] Furthermore, no significant difference was found in major or minor bleeding.[1] TPA is relatively contraindicated in traumatic or prolonged cardiopulmonary resuscitation >10 min because of the risk of massive hemorrhage.[1]

Intracranial hemorrhage is a rare but serious complication of TPA in a patients with myocardial infarction conferring a higher fatality rate and significantly increased morbidity and mortality among the survivors.[30] In the Global Utilization of Streptokinase and Tissue Plasminogen Activator (tPA) for occluded coronary arteries (GUSTO-I) trial, the rate of intracranial hemorrhage was 0.70 % for accelerated TPA therapy.[38] In one study carried out on 71,073 patients from 1484 different hospitals in the U.S with acute myocardial infarction who received TPA as initial reperfusion therapy, 673 (0.95 %) patients were reported to have intracranial hemorrhage with an increased incidence among those with hypertension at presentation (systolic blood pressure more than or equal to 140 mmHg or diastolic pressure more than 100 mmHg), older patients more than 65 years of age, and a history of stroke.[39] Another study has shown an increased incidence of intracranial hemorrhage in those with prior history of intracranial bleeding, use of oral anticoagulant before admission, and body weight less than 70 Kg.[40] Patients more than 65 years old were demonstrated to have a threefold higher probability of cerebral hemorrhage, hypothesized to be secondary to reduced cerebrovascular integrity and an increased prevalence of amyloid angiopathy in this population.[41–47] In our case, the patient's older age and prior history of subarachnoid hemorrhage were deemed to be the responsible risk factors for intracranial bleeding.

The safety of administering intravenous thrombolysis to a patient with a history of subarachnoid hemorrhage who has experienced cardiac arrest has yet to be studied extensively.[34] Stroke guidelines in many countries have enlisted prior history of intracranial hemorrhage as an absolute contraindication for thrombolytic therapy irrespective of the size of bleed, its location or how much recovery has occurred.[34,35] However, one retrospective study carried out on 17,285 patients with acute ischemic stroke, demonstrated no difference in symptomatic intracerebral hemorrhage or 90-day mortality in a small patient sample with a history of cerebral hemorrhage who received TPA.[34] The same study concluded that for a patient with prior intracranial hemorrhage, who had experienced positive recovery, thrombolytic therapy should not be an absolute contraindication, however a low dose of TPA (0.6 mg/kg) should be considered.[34] Prospective randomized controlled trials with larger sample sizes are required for further delineation of the safety of TPA administration in a patient with a history of intracranial bleeding. In our case, it was not clear whether the patient presented with a pre-existing SAH or developed SAH after TPA administration as the patient was in cardiac arrest.

It is very difficult to obtain baseline computed tomography imaging of the head in a patient presenting with cardiac arrest where the emergent resuscitation procedure is a priority.Therefore, there is a lack of evidence to show effective risk/benefit analysis in requiring imaging of the head before TPA administration in cardiac arrest patients. Post-resuscitation care should include discerning the provocative cause of cardiac arrest and treatment of the primary cause of decompensation.[47] Of note, the catecholamine surge associated with diffuse SAH causes ECG changes that may be confused with cardiac ischemic changes. Therefore, non-cardiac causes of ST-segment changes should be considered, especially in patients presenting with non-shockable initial rhythms. In retrospect, the ECG changes in this patient may be consistent with neurogenic ST-segment changes from the SAH. Neuroimaging is commonly pursued in post-cardiac arrest patients for visualization of structural brain injury,[45] however

definite indications of head CT in the resuscitated patients with cardiac arrest remains unknown.[47]

Physicians should consider patient specific risk factors prior to initiating thrombolytic therapy such as the length of time since the intracranial hemorrhage and the recovery condition.[45] Bedside emergency ultrasound has proven to be an invaluable prognostic tool for guiding initial resuscitation and diagnosis of correctable cardiac pathologies in cardiac arrest patients even during chest compressions and cardioversions. This may justify the emergent use of thrombolytic therapy.[48,49] Appropriate age and weight-adjusted dosing of TPA may also limit the risk of adverse consequences of thrombolytic therapy.[49]

4. Conclusion

Thrombolytic therapy in cardiac arrest patient may need to be used on a case-by-case basis, highlighting the necessity for additional research in this area. Knowledge of the strong association to different risk factors and evaluation for patient specific risk factors associated with the development of intracranial hemorrhages are essential for guiding clinical decision making in regards to the use of thrombolytic therapy in cardiac arrest patients of unknown cause.

Conflicts of interest

None.

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