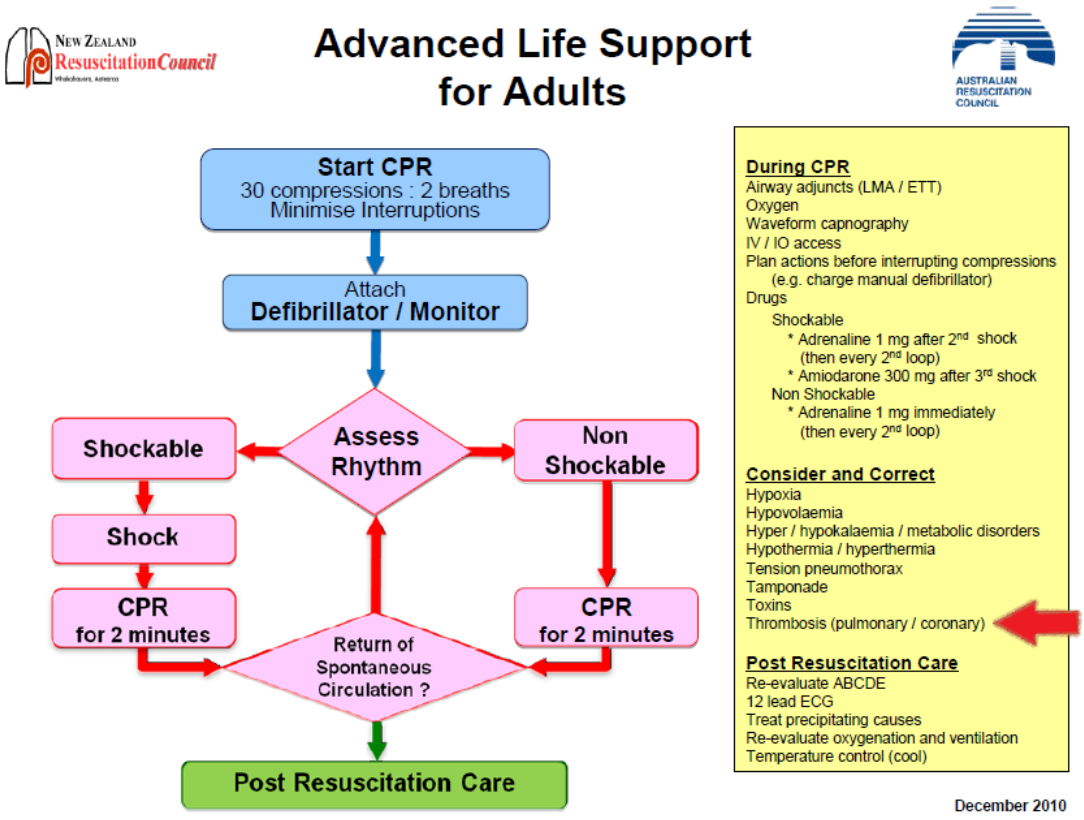
Thrombolysis during Resuscitation – Sydney West Grand Rounds

- ***Introduction:***
  - Autopsy results from cases of unsuccessful resuscitation and coronary angiography in survivors of out-of-hospital cardiac arrest suggest that 50-70% of deaths can be attributed to thrombosis in the form of myocardial infarction or pulmonary embolism. [1,2]

- ***Pathophysiology:***
  - Ischemia and reperfusion during resuscitation from cardiac arrest cause endothelial cell dysfunction, platelet activation, disseminated intravascular coagulation, relatively low fibrinolysis, and a propensity for microcirculatory clot formation. [3, 4]
  - Microcirculatory thrombosis leading to a "no-reflow" phenomenon after return of spontaneous circulation may contribute to poor neurological function after cardiac arrest. [5, 6]
  - Based on the results of the TROICA trial, there seems to be no benefit from the use of tenecteplase without adjunctive antithrombotic therapy in out-of-hospital cardiac arrest. [7]

- ***Current Guidelines:***
  - The current Australian Resuscitation Council ALS algorithm shows the *'Thrombosis (pulmonary / coronary)'* as one of the eight differentials to 'consider and correct' during an ALS. [8]



- However, their 2010 guidelines state: “Routine administration of fibrinolysis for the treatment of in-hospital and out-of-hospital cardiac arrest is not recommended. [Class A; Expert consensus opinion].” [9]
- The American Heart Association 2010 ALS guidelines also state: [10]
  - Fibrinolytic therapy was proposed for use during cardiac arrest to treat both coronary thrombosis (acute coronary syndrome) with presumably complete occlusion of a proximal coronary artery and major life-threatening pulmonary embolism.
  - Ongoing CPR is not an absolute contraindication to fibrinolysis.
  - Initial studies were promising [11-17] and suggested benefit from fibrinolytic therapy in the treatment of victims of cardiopulmonary arrest unresponsive to standard therapy. But 2 large clinical trials [7, 18] failed to show any improvement in outcome with fibrinolytic therapy during CPR. One of these showed an increased risk of intracranial bleeding associated with the routine use of fibrinolytics during cardiac arrest.[7]
  - Fibrinolytic therapy should not be routinely used in cardiac arrest (Class III, LOE B).
  - When pulmonary embolism is presumed or known to be the cause of cardiac arrest, empirical fibrinolytic therapy can be considered (Class IIa, LOE B)."

- ***Trials to date:***
  - **Prospective trials:** [11, 18, 17, 15, 7]
    - 2001, a prospective observational trial of t-PA in cardiac arrest was published by Böttiger et al. [11] This trial was designed to examine the efficacy and safety of thrombolytic therapy in out of hospital cardiac arrest after unsuccessful CPR. The thrombolytic strategy used in this trial was t-PA 50 mg combined with 5000 units of heparin administered over two minutes after 15 minutes of unsuccessful CPR. The control group was comprised of a historical cohort of patients who experienced out of hospital cardiac arrest. This trial was designed to evaluate the safety of the protocol, ROSC and admission to the cardiovascular intensive care unit (ICU). Of the 90 patients included in this trial, 40 were treated with t-PA. Bleeding complications were observed in two patients who both required transfusion due to bleeding from gastric ulcers. There were no bleeding events reported in the control group ($p = 0.379$) and no bleeding complications were related to CPR despite prolonged resuscitation efforts. ROSC was seen in 68% of the thrombolytic group versus 44% of the control group ($p = 0.026$). Admission to cardiac ICU and survival to 24 hours were both improved in the thrombolytic group with admission to cardiac ICU being statistically significant (58% versus 30%, $p = 0.009$, and 35% versus 22%, $p = 0.171$ respectively). Fifteen percent of the thrombolytic group versus 8% of the control group survived to discharge (no p-value provided). This

trial did not distinguish what percentage of their patient population arrested due to PE and it only included patients who were non-responsive to CPR possibly prolonging the time to treatment with thrombolytic therapy. Furthermore, the non-randomized trial design limits the ability to assess the impact of the thrombolytic therapy. In spite of these limitations, this trial suggest a strong association between thrombolytic therapy and improved mortality as well as a favourable safety profile for administration of thrombolytic agents in cardiac arrest.

- Abu-Laban et al published a prospective trail regarding the use of thrombolytic therapy in 2002. [18] This was a randomized, blinded, placebo controlled trial conducted in adult patients with PEA arrest unresponsive to initial therapy. The primary outcome of this trial was survival to hospital discharge. All patients received standard ACLS care and the thrombolytic intervention was t-PA 100 mg infused over 15 minutes versus placebo. Resuscitation was continued for a minimum of 15 minutes after the infusion of the study drug. Two hundred thirty-three patients were enrolled in this trial with 117 assigned to t-PA therapy and 116 to placebo. The primary endpoint was survival to hospital discharge with secondary endpoints including ROSC, hospital length of stay, and bleeding events. One patient in the t-PA treatment arm survived to discharge while no patients in the placebo group survived. No difference was found in rates of ROSC between the tPA and placebo groups (21.4% versus 23.3%, p = 0.99), major hemorrhage (1.7% versus 0%, p = 0.50), minor hemorrhage (0.9% versus 0.9%, p = 0.99), or length of stay (0.4 days versus 0.5 days, p = 0.62). While the results of this trial are not supportive of the use of tPA in non-selected PEA cardiac arrest, the lack of a statistically significant difference with major or minor bleeding is promising for the safety of this therapy in cardiac arrest patients receiving CPR.
- In 2004, Fatovich et al published the results of the TICA trial, which was a prospective randomized blinded controlled trial in out of hospital cardiac arrest, comparing tenecteplase 50 mg as a bolus injection to a matched saline bolus. [17] The primary endpoint was ROSC, with secondary endpoints including survival to discharge from the ED, ICU and hospital. Thirty-five patients were enrolled in this trial with 19 patients in the tenecteplase arm and 16 in the placebo arm. A distinguishing feature of the protocol was the use of thrombolytic therapy as the first agent used in the ACLS algorithm. A significant difference was detected in the primary endpoint with 42% of patients receiving tenecteplase achieving ROSC with only 6% of the placebo group (95% CI 11-61). No statistically significant difference was detected in survival and no bleeding complications were reported. While the difference in ROSC may yield improved outcomes in clinical practice, some key baseline differences between the groups are noteworthy. The

tenecteplase group was significantly younger and had a higher incidence of ventricular fibrillation when compared to the placebo group; these are both characteristics strongly associated with better outcomes after cardiac arrest and may have substantially affected the result seen in the primary endpoint of this trial.

- In 2006, Bozeman et al conducted a prospective observational trial comparing atraumatic cardiac arrest patients unresponsive to ACLS interventions who were treated with tenecteplase weight based dosing versus a control group that presented concurrently without thrombolytic therapy. [15] This trial enrolled 50 patients in the tenecteplase arm and 113 in the control arm to evaluate ROSC, survival to ICU admission, survival at 24 hours as well as hospital discharge. ROSC was achieved in 26% of tenecteplase patients and 12.4% in the control group ($p = 0.04$). No statistically significant difference was noted in survival to ICU admission, 24 hour survival, or hospital discharge. One patient in the tenecteplase group experienced an intracranial hemorrhage. Baseline characteristic differed in that patients in the tenecteplase group were younger and more likely to have experienced witnessed cardiac arrest.
- This issue was evaluated prospectively again in 2008 by Böttiger et al. [7] This trial assessed patients with witnessed out of hospital cardiac arrest due to presumed cardiac causes in a randomized, blinded, placebo controlled trial. The interventions in this group included tenecteplase dosed in a weight-based manner versus placebo. The primary endpoint evaluated 30 day survival and secondary endpoints included survival to hospital admission, ROSC, survival at 24 hours and discharge, and neurologic outcome. The trial enrolled 1050 patients with 525 in each group. No difference was observed in the 30 day survival outcome between tenecteplase and placebo (14.7% versus 17.0%, $p = 0.36$). Additionally, no difference was observed in the secondary endpoints of survival to hospital admission, 24 hour survival or ROSC. Similar results were observed between the groups for neurologic outcomes. Safety endpoint showed significantly more intracranial haemorrhage (symptomatic and non-symptomatic) in patients who received thrombolytic therapy (2.7% versus 0.4%, Risk ratio 6.95 [95% CI 1.59- 30.41]). A subgroup analysis conducted in this trial showed that the placebo group demonstrated improved outcomes in patients presenting with ventricular fibrillation. In the subgroup of patients who were presumed to have experienced cardiac arrest secondary to PE, 2 of 15 (13.3%) were alive at 30 days in the tenecteplase group while 0 of 22 presumed PE patients in the placebo group survived ($p = 0.31$). The analysis of the presented prospective clinical trials suggest that thrombolytic therapy will be beneficial in carefully selected cardiac arrest patients with the cause of cardiac arrest presumed to be secondary to PE.

- **Retrospective trials**: [14, 19, 20]
  - In 2001, a large retrospective observational trial was conducted in patients who suffered atraumatic out of hospital cardiac arrest. [14] This trial was designed to evaluate the impact of thrombolytic therapy on ROSC and hospitalization and excluded patients with obvious non-cardiac disease as the cause of their arrest. Use of t-PA was optional. The thrombolytic agent used in this trial was t-PA dosed as a 15 mg bolus followed by 50 mg infused over 30 minutes then 35 mg infused over 60 minutes and was administered in 108 patients. Two hundred sixteen patients matched for baseline characteristics and not treated with t-PA during resuscitation served as controls. Baseline characteristics differed between the groups with the control group being significantly older than those who received t-PA therapy. Of the individuals treated with t-PA, 65 had a presumptive diagnosis of an acute myocardial infarction and 19 were presumed to have massive PE. Of the total intervention population, 70.4% experienced ROSC, compared to 51.0% of controls ($p = 0.001$). Forty-eight percent of patients treated with t-PA survived 24 hours (versus 32.9% of controls, $p = 0.003$). When looking specifically at patients with a presumptive diagnosis of PE, 57.9% survived 24 hours and 31.6% survived to discharge, corresponding data was unfortunately not presented for the control population. Adverse events attributable to thrombolytic therapy were evaluated in patients with 45 available for autopsy. At autopsy, six of these patients had serious bleeding events; however, the number of patients with intracranial hemorrhage and cardiac tamponade was similar between the thrombolytic and control groups.
  - In 2011, Renard et al. performed a retrospective study in which the primary endpoint was survival to hospital admission. [19] Among 5,102 patients with OHCA in Paris and the suburban area who received medical care from the Fire Brigade of Paris, 1,261 met the following inclusion criteria: age above 18 years with non-traumatic OHCA. Among 107 patients who received FT, 51 (47.7%) survived to hospital admission whereas 272 out of 1,154 (23.6%) patients who did not receive FT survived to hospital admission. A matching process based on a propensity score used to equalise potential prognosis factors in both groups demonstrated that FT was associated with more frequent survival to hospital admission (OR adjusted: 1.7; CI 95% [1.09–2.68]). This result was observed particularly in patients who were not initially shocked by automatic electrical defibrillator (AED) (ORa = 3.61; CI 95% [1.88–6.96]). This study showed that fibrinolysis was associated with improved survival to hospital admission, after performing a propensity analysis. FT may be beneficial in out-of-hospital arrest patients. However, any conclusions drawn are limited by the retrospective nature of the study.

        - In 2008, in two physician-manned emergency medical service (EMS) units in Berlin, Germany, using thrombolysis was based on an individual judgment of the EMS physician managing the CPR attempt. [20] In this retrospective analysis over 3 years (total 22.164 scene calls), thrombolysis was started at the scene in 50 patients during brief intermittent phases of spontaneous circulation, and in 3 patients during ongoing CPR. On-scene diagnosis of myocardial infarction was established in 45 patients (85%) by a 12-lead ECG, 5 (9%) patients had a left bundle branch block. Sixteen patients (30%) died at the scene, 37 patients (70%) were admitted to a hospital. In-hospital mortality was 35% (13 of 37 patients), with cause of death being cardiogenic shock in nine patients, hypoxic cerebral coma in two and acute haemorrhage in two other patients. All 24 of 53 (45%) survivors were discharged with an excellent neurological recovery. CPR was started by an EMS physician in 18 of the 24 survivals (75%) and emergency medical technicians who arrived first in six (25%). Duration of CPR until return of spontaneous circulation was <10 min in 13 of 24 (54%) of the survivors. Thrombolysis was initiated during intermittent phases of spontaneous circulation in 50 (94%) of all patients and in 23 (96%) of the 24 survivors. The authors concluded that this retrospective analysis shows excellent survival rates and neurological outcome in selected patients with a high likelihood of myocardial infarction, who develop cardiac arrest and are treated with thrombolysis.

- ***Case reports*** from the PE-arrest-tPA world showed that tPA was still safe after up to 22-75min of continuous CPR [21, 22, 23, 24] & up to 1-2 days of intermittent CPR + therapeutic hypothermia + intra-aortic balloon pump in one patient. [25] Another patient who had had a haemorrhagic stroke 8 weeks prior to PE-arrest tPA remained free of any bleeding complications until her discharge several days later. [26]

- ***Conclusions:***
    - The current (2010) guidelines do not support a routine use of tPA during resuscitation. [9, 10]
    - There is no worldwide consensus on a tPA dosing & administration protocol for cardiac arrests or peri-arrests. [27]
    - We have only had one study from after the 2010 time period. This retrospective study suggests a benefit from tPA during cardiac arrest. [19]
    - Three prospective studies and several case reports from both the IHD-arrest the PE-arrest fields showed a lower risk of a major bleed following a tPA administered during CPR &/or weeks away from a haemorrhagic stroke. [11, 17, 18, 21-26]
    - Despite the large prospective study of Böttiger et al in 2008 showing an increased risk of ICB in the thrombolytic group, the latter group also showed an improved outcome when compared to the placebo

group, which highlights the question of which patients group are to be considered safe to thrombolyse. [7]

- A recent comprehensive evidence review by Logan et al. has recommended that the majority of cardiac arrest secondary to pulmonary embolism must receive thrombolytics because *'outcomes are uniformly poor.'* [27]

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