

PULMONARY EMBOLISM THROMBOLYSIS



“The Crocus Gatherer”, Minoan fresco from Akrotiri, Santorini, 2nd millennium BC, National Museum Athens...is this the face of Atlantis?

“...And then suddenly, as they moved swiftly over the great Cretan deep, they were terrified by the night they called, “a pall of darkness”. Neither stars nor moonlight pierced the obscurity. The black chaos was coming down from the sky, or some other form of darkness was rising from the innermost recesses of the Earth. They had no way of knowing whether they were voyaging in water or through Hades. Helpless they could only entrust their safe return to the sea that was carrying them. In this extremity Jason prayed to Apollo, and the god guided them with the glint of his bow to Anaphe, east of Thera, where they landed and sacrificed in sunshine once more...”

*The Argonautika, (Jason and the Argonauts)
3rd Century B.C, Bk IV 1684-1716.
Apollonios of Rhodes (c. 305-235 B.C)*

One of the most haunting legends from deep antiquity is that of the lost city of Atlantis, a story passed down through countless generations before the dawn of literate civilization. The story of this lost city persisted in the psyche of the early Mediterranean world, like a faint memory from early childhood, only partially recollected and incompletely understood. And like a child’s memory it was an impression more so than actual detail that was recalled. That impression was one of nightmare, of Armageddon. An event had occurred that appeared to be the end of the world, an event of unimaginable terror and as a consequence of it, the greatest city on the Earth was consumed in flames and then sunk into the oceanic abyss, disappearing without a trace, as though it had never existed.

Many centuries passed, until by the time of a more sophisticated and literate society, debate raged as to whether or not this event had been real or was merely a myth. No less a figure than Plato himself, however insisted that the story was based on fact. He claimed that 300 years before his own time a Greek traveller to Egypt by the name of Critias had seen with his own eyes a written description of the event carved in hieroglyphics on an ancient stone column. Yet doubt about the authenticity of the legend persisted, from Plato’s time to the modern era.

In modern times two electrifying discoveries have revived the legend of Atlantis, one an archaeological discovery, the other a geological one. In the 1860s a Bronze Age Pompeii was discovered at Akrotiri on the Greek island of Santorini. Underlying the pumice that was being mined to create cement to be used in the construction of the Suez Canal were the remains of a long lost Minoan civilization complete with very sophisticated frescos of labyrinths, bulls, Minotaurs and all manner of symbolism associated with the Minoan civilization of Crete that had disappeared abruptly and without apparent cause in the mid second millennium B.C. Ongoing geological investigation of the volcanic island of Santorini has since revealed that a titanic eruption occurred around the year 1640 BC. By some accounts the energy released by this eruption would have been ten times that of the eruption of Krakatoa in 1883. There is now further evidence that a truly stupendous tsunami occurred as a result of the eruption. This tsunami hit the coastline of Crete, devastating the Minoan civilization that lived there at the time to such an extent that it simply disappears from the written record. The volcanic ash that came from such an eruption would have plunged the Mediterranean world into darkness for months if not years.

To a superstitious pre-literate and pre-scientific society this event would have been seen as the end of the world and only one explanation would have been possible...the furious wrath of the gods. The story was passed down from generation to generation in the form of legends and myths that reflected the earliest memories of the civilizations of the eastern Mediterranean. One of the most ancient stories handed down through untold generations was finally put into writing during the third century BC. This story was so ancient it was even acknowledged by Homer in the Eighth century BC, as a "story well known by all". It was the story of Jason and the Argonauts, and ranks along with the Sumerian epic of Gilgamesh and the biblical story of Noah's flood as an echo of humanity's earliest memories. Many archaeologists and ancient historians of today are convinced, as was Plato in the Fourth century BC, that aspects of these stories have their basis in long forgotten truths. The story of Jason and the Argonauts reflects one of humanity's most fundamental traits, the quest for exploration and knowledge. It is thought that the story of Jason recollects humanity's first tentative exploration of the seas of the Mediterranean and the Black Sea. And like the earliest memories of a far distant childhood, they are incomplete, confused and mysterious, but the sentiments are very real. In a fascinating passage of the fourth book the Argonauts glide across still the waters of the "great Cretan deep", just "east of Thera", when the whole world is suddenly plunged into a "pall of darkness" that has appeared to have erupted from the "innermost recesses of the Earth". They think they may have been transported to Hades. In another passage they are pummeled by enormous boulders hurled at them by the giant Talos. They are convinced that the gods are against them and cry out to Apollo to guide them back to the light. Are these echoes of the terrifying experience of the Minoan eruption of Santorini recorded in the story of the Argonauts? Is the world enveloping "pall of darkness" the ash clouds of a volcano? Are the boulders of the giant Talos, the molten rocks flung from its interior? Was the Minoan civilization of Thera terminated by the eruption of Santorini the basis of the legend of the lost city of Atlantis? Unfortunately, like the memories of childhood the exact facts will probably never be known, yet the anecdotal stories do convey a very real legacy, a universal constant of the human condition... the terror of Armageddon. The evidence to conclusively prove the legend unfortunately will probably never come to light, yet the anecdotal archeological and geological evidence for the story is nonetheless, compelling.

It is said that those who have the misfortune to suffer a massive pulmonary embolism, experience a primal response of the human condition, a feeling of "impending doom", their own Armageddon. Clinicians of the 21st century will be placed in a particular dilemma. In the scientific age we strive to make our decisions according to the scientific "evidence base", yet in many cases this base simply does not exist to guide us. We are as lost as the Argonauts who set out to explore the unknown world. When this evidence does not exist we must use our clinical judgement. For patients who suffer sub massive pulmonary embolism the situation is dire. Virtually all Emergency physicians can however recount an anecdotal story of thrombolytic success in these cases, yet the strict scientific evidence base does not exist with respect to improvement in mortality when using this treatment. Thrombolysis is not without risk, yet the patient hovers close to death. In some cases in medicine management will of necessity be based on the anecdotal evidence. It may in fact be the case that, like the legend of Atlantis the evidence may never be available to us and compelling anecdote will remain our best guide.

PULMONARY EMBOLISM THROMBOLYSIS

Introduction

Pulmonary embolism may be considered in 3 groups:

1. Uncomplicated pulmonary embolism:

- The clot burden is not large, there is no hypotension and there is no evidence of RV strain.

2. Sub-massive pulmonary embolism:

This can be defined as pulmonary embolism that does not have hypotension but does have:

- A large clot burden (around 50% or more as assessed by radiologist on V/Q or CTPA)

And/ or

- Evidence of RV strain.

3. Massive pulmonary embolism:

- Here there is cardiogenic shock, usually defined as hypotension with a systolic blood pressure < 90 mmHg.

Pathophysiology

Note that in otherwise healthy individuals a clot burden of around 50% or more of the pulmonary circulation will be required before significant compromise of the circulation occurs.

However it should be noted that clot burden is not the only factor which will determine the degree of cardiovascular compromise. Other important factors will include the release of neurohumoral factors that result in vasoconstriction in non-embolised segments of the lung and the degree of pre-existing cardiopulmonary disease.

RV Strain

Patients who have pulmonary embolism and evidence of RV strain (with initial normal blood pressures) are at increased risk of progression to cardiogenic shock.

Indicators of RV strain include:

1. ECG changes:

- Dominant R waves in early V leads with non specific ST changes.
 - Right bundle branch block type patterns.
 - Right axis deviation.
2. Troponin levels:
- Elevated without evidence of STEMI
3. **Echocardiography:**
- This is the best investigation as it is the *most sensitive and specific*.
 - RV strain will be evidenced by acute right ventricular dysfunction and/ or severe pulmonary hypertension.
 - **It should be done when clot burden is high, or the ECG shows evidence of new RV strain or troponin levels are elevated.**

Management

Pulmonary embolism with shock:

For patients with pulmonary embolism and shock and without an absolute contra-indication to thrombolysis, the treatment is thrombolysis:

1. Reteplase²
 - 10 U bolus IV followed by second 10 U bolus IV in 30 minutes.
2. Heparin
 - Give an initial 5000 unit IV bolus dose with the first reteplase dose and commence heparin infusion with the second reteplase bolus dose as per the hospital heparin infusion protocol.

Ongoing heparin infusion and subsequent warfarin therapy should then be according to the standard hospital guidelines for these drugs.

All patients who have received thrombolysis for PE are to be admitted to HDU/ICU.

Pulmonary embolism with cardiac arrest:

Bolus reteplase therapy should be given during resuscitation attempts in patients with cardiac arrest.

Pulmonary embolism with evidence of RV strain or large clot burden:

This is an area of uncertainty. Controversy exists concerning whether these patients should be treated with heparin or with thrombolysis.

Most current opinion suggests that they should be treated with IV heparin or SC enoxaparin according to the standard hospital protocols. However they need to be carefully monitored for any sign of deterioration.

Some medical opinion advocates the use of thrombolysis in these cases, even though improvement in mortality has not been conclusively demonstrated. Each case needs to be considered on its own merits however and in some cases thrombolysis may be considered if:

- Clot burden is very large (> 50%)

And/or

- There is supporting evidence of RV strain, particularly on echocardiography

And

- The patient is not at high risk of cerebral haemorrhage.

The final decision to thrombolyse in these cases should be in consultation with ICU/ ED consultants/Respiratory unit. Where possible informed consent of the patient should also be sought.

Patients who are treated with heparin yet have evidence of large clot burden or RV strain should be **discussed with ICU**. These patients are at increased risk of developing hypotension (probably due to clot extension), in which case “secondary” thrombolysis will need to be considered. **It is for this reason that admission to HDU/ ICU will be advisable in most of these cases.**

Uncomplicated pulmonary embolism

These are treated with IV heparin or SC enoxaparin and warfarin according to standard hospital protocols.

These patients may be admitted to a general ward or SSU bed and suitable candidates later referred to the HITH program.

Additional Considerations

1. Central venous and intra-arterial lines are not essential prior to thrombolysis. The need for these lines should be discussed with the ED or ICU consultant in each case as they may not be necessary in the first instance and carry some risk in this setting.

2. The generally accepted contraindications to thrombolysis should always be weighed against the risk of death from PE.

It should also be noted that the risk of serious hemorrhage is somewhat higher when thrombolysis is used for PE as opposed to MI.

See reversal of thrombolysis guidelines for the contraindications to thrombolysis as well as risk factors for intracerebral hemorrhage.

3. Patients who have compromised RV function and significant amounts of in situ peripheral clot (ie above knee DVT) may be candidates for an IVC filter, as clinical reserve in these cases would not be expected to be great. This issue will generally be addressed by ICU in conjunction with the vascular surgical unit.

References

1. International Pulmonary Embolism Registry: Lancet 1999; 353: 1386-89.
2. Tebbe et al. Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. Am Heart J 1999, 138:39-44

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