CASE REPORT

Controversy and consent: achieving patient autonomy in thrombolysis for acute submassive pulmonary embolism

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SUMMARY

Acute pulmonary embolism (PE) is associated with a wide variation in patient outcome ranging from completely asymptomatic to cardiac failure and death. This presents a challenge to clinicians in ensuring the correct treatment for individual patients is given and that adverse events secondary to treatment complications are minimised. The evidence for those with massive PEs and non-massive PEs is clear for and against the use of thrombolysis, respectively. However, in those with 'sub-massive' PE there is no clear consensus on whether there is a treatment benefit. We present the case of a patient who presented with a non-haemodynamically significant PE but with evidence of right ventricular dilatation, and discuss the difficulties in treatment decisions in such cases, including the ethical and legal principles of consent, and how clinicians might best allow their patients to make informed decisions when in clinical equipoise.

BACKGROUND

Venous thromboembolic disease is common, with a reported incidence of 23–69 per 100 000 people/year, and encompasses a wide range of potential clinical scenarios, ranging from patients with asymptomatic deep vein thrombosis (DVT) to those with lethal massive pulmonary embolism (PE).¹ While diagnosis of venous thromboembolism (VTE) represents its own clinical challenges (discussed in depth elsewhere), its treatment can be challenging in certain situations.²

The American Heart Association (AHA) classification is commonly used to classify PE. 'Massive PE' includes those with sustained hypotension <90 mm Hg systolic for >15 min, or those with signs of shock or requiring inotropic support. 'Sub-massive PE' includes those without the above symptoms but with evidence of right ventricular (RV) dysfunction on ECHO or CT and/or myocardial necrosis (eg, raised troponin). 'Non-massive PE' covers all diagnosed acute PE with none of the above markers of severity.^{3 4}

Data from a large multicentre prospective registry of more than 15 000 patients presenting with VTE gave a 3-month mortality rate secondary to PE (excluding other causes) of 1.68%.⁵ While the majority of the patients with VTE had a DVT or non-massive PE, out of those 1.68% of patients who died from a PE, 71% fell into the submassive PE category. This indicates that the specific subset of these patients accounts for a significant

proportion of deaths secondary to PE, and that this is therefore not an uncommon clinical situation, with potentially harmful consequences, to encounter.

Following the landmark Lancet trial in 1960, there is strong evidence for anticoagulation with low-molecular-weight heparin (LMWH) or a coumarin (in absence of contraindications) in patients with VTE including acute PE.^{4 6 7} However, the evidence for the use of thrombolytic agents is less clear; whereas anticoagulation primarily prevents further thrombus formation, thrombolytic drugs activate the fibrinolytic cascade thereby promoting active clot degradation, but at the additional increased risk of haemorrhage.⁸ While in those patients with massive PE thrombolysis is associated with a statistically significant reduction in recurrent PE or death, and in those with non-massive PE thrombolysis may confer an increased risk of mortality and is therefore not indicated, the evidence for those with submassive PE is unclear currently and leaves clinicians in clinical equipoise.^{4 9–11}

CASE PRESENTATION

A 59-year-old woman presented on the acute medical take with worsening shortness of breath over a period of 3 weeks. She described a history of shortness of breath initially on exertion; however, this became increasingly severe and, at the time of presentation, even occurred at rest. She described right-sided pleuritic chest pain coinciding with her dyspnoea, but in the absence of syncope, palpitations or central chest pain. There was neither haemoptysis, nor calf swelling, previous DVT/PE, family history of thrombosis/recent travel, nor was there immobility. The patient had no 'red flag' symptoms suggestive of underlying malignancy. Her medical history included hypertension, osteoarthritis and primary hyperthyroidism. She took losartan 100 mg once daily and levothyroxine 75 µg once daily. There were no reported drug allergies. She was independent and lived with her partner.

On examination, she was dyspnoeic at rest, with a regular heart rate of 95 bpm. She had an oxygen requirement (2 L via nasal specs) to maintain SpO₂ between 94% and 98%. Her heart sounds were normal and jugular venous pressure was not visibly raised; she had a blood pressure of 148/91 mm Hg. No other abnormalities were found on examination other than a large body habitus.

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INVESTIGATIONS

Admission blood tests revealed significantly raised D-dimer (2429 ng/mL). Full blood count, and urea and electrolytes, were unremarkable (haemoglobin 150 g/dL, white cell count 10.5×10^9 , estimated glomerular filtration rate/1.73 m² of >90). Arterial blood gas analysis on 2 L/min O₂ showed a pH of 7.42, pCO₂ 4.7 kPa (normal range 4.6–6 kPa), HCO₃⁻ 20.6 (normal range 21–26 mmol/L) and pO₂ 8.8 (normal range 10–13 kPa), and lactate 1.76 mmol/L (normal range <4 mmol/L).

Plain chest radiograph showed no abnormalities and 12-lead ECG showed sinus rhythm with isolated T-wave inversion in lead V3 only.

CT pulmonary angiogram demonstrated large PE in both central pulmonary arteries extending into all lobar arteries bilaterally, with evidence of RV outflow obstruction and features suggestive of pulmonary hypertension.

TREATMENT

Following diagnosis of PE with signs of RV outflow obstruction and pulmonary hypertension, discussion was had with the respiratory team and a tertiary cardiothoracic centre. Given the absence of haemodynamic compromise to classify the patient as having massive PE, but with signs of RV failure, it was felt by the treating consultant that thrombolysis, in addition to LMWH, may reduce the risk of cardiac failure in the long term. The lack of strong evidence for this indication was, however, highlighted, and other team members were concerned that this was not indicated. A discussion was had with the patient to attempt to convey this uncertainty in addition to the possible benefits, including decreased risk of cardiac failure, but also the risks of bleeding, including intracerebral haemorrhage and subsequent persistent neurological deficit. The patient was hesitant when faced with the risk of stroke, however, she agreed to proceed with the treatment on the basis that she might have a quicker recovery with less chance of long-term cardiac complications.

After verbal consent to proceed, 10 000 units of tenecteplaseⁱ (Metalyse) were administered, and the patient was monitored in the acute care unit.

OUTCOME AND FOLLOW-UP

Following administration of thrombolytic therapy, observations remained stable and neurological examination unremarkable. The patient reported feeling markedly less dyspnoeic by the following morning and had no complications from her treatment. A CT of the abdomen and pelvis was performed and showed no evidence of malignancy as a precipitating factor for the PE. The patient was discharged 3 days later with anticoagulation and outpatient haematology follow-up appointments with no evidence of haemorrhage or clinical signs of cardiac failure.

DISCUSSION

This case highlights the challenges of managing patients with submassive PE, both in terms of the conflicting evidence for thrombolysis in this situation and the complexity of communicating the available evidence to patients. We shall therefore discuss the evidence for and against thrombolysis in this subgroup, and examine how to use the available data in order to best achieve individualised decisions regarding thrombolysis in these patients.

Thrombolysis in submassive PE has not shown a clear mortality benefit in studies so far. The recent (and largest) multicentre Pulmonary Embolism Thrombolysis (PEITHO) randomised controlled trial (RCT) included over 1000 patients and did show a statistically significant OR of 0.44 (0.23 to 0.87) for the composite primary outcome measure of death or haemodynamic decompensation within 30 days in those randomised to thrombolysis, however, when death alone is analysed the OR becomes non-statistically significant at 0.65 (0.23 to 1.85) with a p value of 0.42.¹²

There is evidence to suggest that thrombolysis does improve early RV function and clot resolution, which results in increased haemodynamic stability initially. Furthermore, it is theorised that this effect may reduce the risk of long-term complications such as chronic thromboembolic pulmonary hypertension (CTEPH).¹³ However, there is also evidence to suggest that the effect on RV dilation is transient and lost within 48 h post-thrombolysis.¹⁴ The largest RCT, aforementioned, did not measure outcomes, such as CTEPH, past 30 days, and there are scant data to evaluate this in other studies. We therefore do not know conclusively if thrombolysis in submassive PE is of benefit in preventing long-term complications.

The significant risk associated with thrombolysis is, of course, haemorrhage. The risk of haemorrhagic stroke is consistently around 2% among haemodynamically stable patients, according to the existing data.¹² We know that this risk increases with age (>75 years), however, the risk of mortality from PE also increases with age and other comorbidities, such as cancer and neurological disease, causing immobility.¹⁵ Box 1 further elaborates on risk factors for mortality in VTE.

In this scenario it was therefore unsurprising that there were differing views between clinicians—the evidence as summarised above is inconclusive but shows advantages and disadvantages to both treatment options. This case therefore reflects the natural difficulty of treating when in equipoise. In this situation, it is important that clinicians should consider first and foremost how to present these risks and benefits in a way that is understood by the patient, allowing the patient to make an informed decision based on both the available facts (table 1 and box 1), and in the context of the patient's preferences and values. But how should

Box 1 Patient information summarising the current evidence for thrombolysis in submassive pulmonary embolism (PE)

- ▶ The risk of death from this type of PE is around 2%, that is, 49 of every 50 patients will survive. The risk of death, however, increases with increasing age and concurrent medical conditions
- ▶ There is no clear evidence that thrombolysis (use of 'clot-busting' drugs) reduces this risk of death when used in addition to the standard treatment, but it may reduce the load on the heart in the short term by breaking down the clot more quickly
- ▶ Thrombolysis, however, increases the risk of bleeding—1 in 5 patients will have significant bleeding, with around 1 in 50 patients having a bleed in the brain (a stroke), which may cause lasting weakness or other impairment. Conversely, this means 49 of every 50 patients will not have a bleed in the brain

ⁱUnlicensed indication.

Table 1 Risk factors associated with increased or decreased mortality in patients with VTE⁵

Risk factors for higher mortality in those with VTE	Risk factors for lower mortality in those with VTE
<ul style="list-style-type: none"> ▶ Immobilisation for neurological disease (ie, stroke) ▶ Age ≥75 years ▶ Co-existing cardiac or respiratory disease ▶ Cancer 	<ul style="list-style-type: none"> ▶ Increased body mass index ≥30 kg/m² ▶ Recent surgery ▶ History of VTE ▶ Male

VTE, venous thromboembolism.

this decision be discussed and documented, given the complexities of the evidence base and the variation in patients' preferences and circumstances?

Legally, for patients to be able to consent to a procedure, doctors in England have a duty to inform patients of the level of necessity of the procedure, of possible alternatives and of any common or serious consequences. Failure to do so may result in prosecution.¹⁶ This differs to US law, where valid consent requires patients to be given all material facts necessary for *the patient* to give valid consent—"The scope of the physician's communications to the patient, then, must be measured by the patient's need...[a] risk is thus material when a reasonable

person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy."¹⁷ This view is similar to the guidance issued by the General Medical Council (GMC), in which the informed consent is tailored to the patient's individual circumstances.¹⁸ It seems that the examples from both US law and GMC guidance seem most applicable to situations where there is clinical equipoise in which the values and social context of the patient's life have significant weight in the treatment decision, given that the evidence for benefit does not add significant weight to either side.

We must consider then, that patients may have widely differing views on what they deem to be an acceptable level of risk and, additionally, that the impact of complications on quality of life is a subjective one—the potential 2% risk of intracranial haemorrhage and therefore potential loss of speech, motor or other cognitive function, may for some be considered as outweighing the theoretical chance of reducing the 2% chance of death or the risk of heart failure. Others, however, may feel the long-term benefits of the potential for improved cardiac function and possibly overall survival outweigh the increased risk of stroke and other bleeding risks. Clinicians must be aware that patients will react differently to each of these risks, and should try to place these risks in the context of the patient's life—for instance, by considering that a patient who relies on fine motor skills (eg, a concert pianist) may feel very differently about the potential (even if very minor) of motor weakness or incoordination associated with thrombolysis, while this might not impact a different patient who is in different circumstances.

Respect for autonomy is one of the founding principles of current medical practice. We acknowledge that patients have the right to decide if they wish to have treatment, and that, where there is no uncertainty with regard to their capacity ('assumed capacity' is the default state), patients may refuse treatments even if felt to be in their best interest by medical professionals.^{18 19} However, to be able to consent to a procedure, patients must be presented with enough information for them to make an informed decision. We suggest that, as described above, clinicians discuss the possible benefits and risks of thrombolysis within the context of the patient's individual circumstances, taking into account their other risk factors, comorbidities, social situation and preferences, and emphasising that there is no 'right' answer. A period where the patient has time to reflect alone or with family, and consider if they have further questions, may then be useful, followed by time for the clinician to respond to any further questions and ask the patient to summarise the information presented, and to review their understanding of the risks and benefits as relevant to them, and come to a shared decision. This can then be documented clearly in the medical records.

We present a table of relevant risks and benefits of thrombolysis, as guided by current evidence, to aid clinicians in delivering accurate and understandable information to patients as suggested (table 1), but of course the relative importance of these risks and benefits will vary greatly between patients, and clinicians should emphasise this and use new data as they emerge, to tailor their discussion with patients.

We must, however, consider that patients are under considerable physical and mental strain at times such as this. They have a potentially lethal condition, are often in pain and may be severely dyspnoeic. These factors may influence a patient's decision process. They may feel increased pressure to 'do something' or to stop themselves feeling breathless while not considering

Box 2 A suggested flowchart to aid clinicians during the decision-making process

- ▶ Is the patient alert, responsive and able to communicate?
If not: consider a decision made using all available evidence from family and other healthcare professionals, to make a decision in the patient's best interest
If yes: explain the risks and benefits of thrombolysis as relevant to the patient's individual risk profile and personal circumstances. Data from table 1 and box 1 may be helpful. Provide the patient with time for reflection and discussion with family and other professionals. Move on to the second point
- ▶ Is the patient able to communicate their decision back showing consideration for the risks and benefits as explained?
If not: consider suggesting a course of action in the patient's best interest, as above
If yes: consider and discuss the significant physical and mental strain the patient may currently be experiencing. Evaluate with the patient how this may be affecting their decision-making ability, move on to the third point
- ▶ Following the above, does the patient and clinical team feel the patient has capacity to consent?
If yes: proceed as per the patient's wishes. Document the above steps in the medical record
If not: discuss with the patient the risk in proceeding with a procedure that does not have significant evidence for benefit and the risks of side effects—explain that this is not a decision to rush into under significant physical and mental burden. It may be prudent to allow more time for ongoing discussion. Involve other members of the multidisciplinary team and preferably other clinicians in order to propose a suggested course of action to the patient. Document this in the medical record

the risks of such treatment in the long term. This issue has been previously discussed in relation to thrombolysis for acute stroke, and indeed a patient (and barrister) describes how he felt both personally and legally, that he was not in a position to give informed consent at the time due to the significant physical and mental strain he was under during his period of acute illness.¹⁵

If clinicians are concerned that a patient does not demonstrate a suitable level of understanding of the risks and benefits in order to make an informed decision even after all attempts to explain the information in a patient-specific manner have been made, or indeed if the patient informs that he or she does not want to make the decision, it must be considered that the patient's doctors have a duty of care to the patient and should propose a recommended course of action based on what they feel is in the patient's best interests (taking into account the evidence in addition to the individual patient's risks, comorbidities, values and social circumstances, as described earlier) and explain to the patient why this is so. Clinicians should respect autonomy but be cautious not to 'hide' behind autonomy as a reason not to propose a course of action if after careful discussion it is evident that the patient is unable to demonstrate sufficient understanding of the decision he or she is making. Box 2 details a suggested flowchart for clinicians, summarising the steps recommended above.

There are many situations in medicine when the evidence does not clearly support one treatment over another. In such cases, knowledge of the existing literature, and the tools and skill to present this to patients in a way that is understood, especially when treatments can have significant consequences, is

essential. While it can be argued that patient autonomy can never be absolute, and consent can never be fully informed, we must strive towards the complex task of both, understanding the available data and presenting these in a context-specific manner to facilitate, wherever possible, patient choice; but we must also be ready to step in and propose a course of action where it is in the patient's best interest to do so. Finally, when physicians disagree over a course of treatment, this should be seen as a trigger to further engage the patient in the final decision.

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Learning points

- Venous thromboembolism as a diagnosis encompasses a wide range of clinical scenarios for which optimal treatment varies. In the subgroup of patients that have 'sub-massive' pulmonary embolism, the evidence showing benefit of thrombolysis is unclear—this leaves clinicians in equipoise.
- Submassive PE patients are defined as those without evidence of haemodynamic compromise (systolic >90 mm Hg for 15 min or requiring inotropic support) but with evidence of right ventricular dysfunction on ECHO or CT and/or myocardial necrosis (eg, raised troponin).
- Where it is unclear whether a treatment will benefit patients, such as discussed here with thrombolysis in those with submassive PE, open discussion with patients must be encouraged and data presented in an understandable way, and, where possible, tailored to the patient's unique risk profile.
- Clinicians should be aware of the current guidance from the General Medical Council and other regulatory bodies concerning consent and capacity, and that discussion with patients regarding the risks and benefits should be conducted in a personalised way and documented clearly in medical records.

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