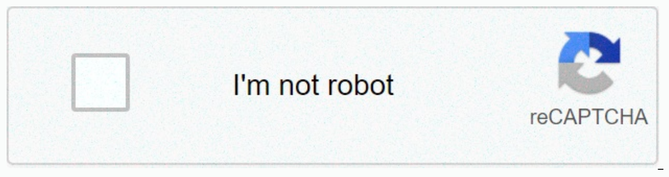

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Submassive pe treatment guidelines

Pe is a humble disease. This is a highly heterogeneous disease, covering the range of patients who are doing quite well to patients who are deeply ill. To further complicate matters, patients can evolve rapidly in one direction or the other. Since PE is a heterogeneous and emerging condition, it should come as no surprise that our evidence base is far from complete. This is a good example of the common lumping-vs-splitting paradox in finding many critical diseases: If we acoct patients with different severity together, then the results become difficult to interpret (perhaps the study intervention is helping some patients within the cohort, but not others). If we divide patients based on severity, then it becomes difficult to recruit a population large enough to study with statistical power. Recently, multidisciplinary PE response teams (PERT teams) have become popular as a strategy to handle this disorder. Pert teams offer patients quick access to numerous different services and the opinions of a diverse group of specialists. A formalized team-based approach is also ideal for collecting data and following patients longitudinally. When available this is an excellent strategy, but most hospitals do not have the resources for this approach. Controversy abounds regarding pulmonary embolism, and will likely persist into the foreseeable future. This chapter includes schemes to give direction to how these patients could be managed (and which are largely consistent with the consensus practices of the PERT consortium) (31185730). However, individual patients are quite heterogeneous, so these concepts must be adapted to the specificities of each patient (including patient preferences). Many unstable patients have PE, but in some cases may have multifactorial instability (e.g. PE plus sepsis plus hypovolemia). Thrombolysis is beneficial only if PE is causing patient instability. Factors to consider are: (1) Clot load in CT scanning In order to blame patient instability in PE, there should be a moderate to large clot load in CT scanning. The precise amount of clot in scanning may not be useful (for example, if the patient has a PE chair). However, if there is only a small amount of clot, PE probably isn't causing the instability. For example, a patient with right ventricular dilation and small clot load may have chronic pulmonary hypertension. (2) Global hemodynamic evaluation with echocardiography Unstable patients due to PE should have at least one dilated lower vein cava and a dilated right ventricle. If the lower vein cava and the right ventricle were not dilated, consider whether another process is causing the (e.g. smaller hypovolenmic shock). Ultimately, clinical judgment is necessary to determine whether a patient's instability is caused by pulmonary embolism. For more information about the shock investigation, see the crash chapter. Once a (sub)massive PE is it is or strongly suspicious, it is useful to immediately get the following study panel. Given the speed of this disease process, it is generally best to get a full panel of laboratories at the helm. Stratification of risk in PE is extraordinarily difficult. Being exhaustive is good, but it is also important to avoid counting the same risk factor several times (for example, if the right ventricle is severely dilated in CT and also dilate in echocardiogram, then echocardiogram really does not provide any new prognostic information). Syncope story or almost synchronope are worrisome (revealing an absence of hemodynamic backup). However, these characteristics can be an independent risk factor when other variables are counted (30339253). The duration of symptoms is important: Having symptoms >10-14 days suggests a more chronic thrombin (over time, clots are organized and become less sensitive to thrombolysis). Having stable symptoms for several days reduces the likelihood of sudden deterioration. Symptoms of recent onset or acceleration are worrying. general appearance (0) A sense of imminent condemnation is worrying. If the patient volunteers a feeling that they are dying, they are often right. (1) Diaphoresis is very worrying (this reflects the secretion of endogenous epinephrine keeping the patient alive). (2) Signs of hypopoperfusion are the most worrying: Mottling (especially diffuse mottling) Cold Limbs Confusion, vital signs of Bradycardia agitation is the most worrying may be a germ of imminent Brady-Asystolic detention (often as these patients die). Tachycardia is also worrying A shock index (heart rate/systolic blood pressure) higher than one suggests poor hemodynamic reserve and worse prognosis (30638984, 27800569, 27742425, 27107684, 25743032, 24973834, 23168283, 19649996, 18308025, 17804446, 12581684). Hypotension is traditionally the main parameter used to define massive pe. Any of the following criteria would generally be defined as a massive PE: (i) Systolic blood pressure < 90 mm for 15 minutes (ii) Drop in systolic blood pressure in >40 mm for 15 minutes (iii) Requirement for vasopressants. Hypertension is generally reassuring , but not always. A small subset of PE patients have a lush release of epinephrine that leads to hypertension (essentially overcompensation for their PE). These patients are hypertensive, but they look and feel horrible (e.g. diaphoretic, tachycardiac, clammy) and often have high lactate. These patients should probably be classified as high-risk submassive PE. Tachypnea In general, the respiratory rate is an excellent predictor of hidden critical illness and subsequent deterioration (18513176). Severely high respiratory rate (e.g. >30 breaths/minutes) has correlated with worse (27800569, 23168283) high troponin correlates with mortality risk (with a probability ratio of ~5)(25976228). Studies have used a wide range of troponin cutting values (25976228). Taking into account the available body of literature, literature, cutting values could be Troponin I >0.1 ng/ml or Troponin T >0.03 ng/ml (16018861, 17606843). However, keep in mind that values close to these snippets can actually represent a gray area. These values do not really provide any useful information (neither increase nor substantially reduce the patient's risk). Lactate lactate is a strong predictor of mortality. In general, it is probably underutilized in risk stratification. A high lactate generally reflects aerbic hyperlactatemia due to the production of endogenous epinephrine. This reveals that the patient is under hidden hemodynamic stress, and is trying to compensate for this stress through greater sympathetic output. Lactate essentially functions as an endogenous sympathetic tone marker. Right ventricular dilation and EKG signs of strain RV CT signs [1] RV dilation (isolated mild RV dilation does not have a great specificity for true VR dilation in echocardiogram)(21835376, 27664798). If VR dilation in CT is equivocal, additional signs of VR dysfunction should be sought either in CT or echocardiography. [2] VR tilt in LV. This can be better observed in a coronal CT projection (as with echocardiography, multi-flat heart evaluation can improve diagnostic accuracy). [3] Contrast reflux in the lower vein cava and liver veins. Echocardiographic signs [1] VR dilation[2] Systolic RV failure (tricuspidic valve reduction ring systolic excursion). McConnel signs (VR-free wall hypokinesia) can also be pointed out, but the amount of independent information this provides is unclear. Contrary to popular belief, the McConnel sign is not entirely specific to PE, but can also be seen in the right ventricular myocardial infarction. [3] Paradoxical change of the interventilationcular septal (RV pressure overload). [4] The clot in transit seen in the right ventricle increases the likelihood of PE-related death by a factor of five (ESC 2019 guidelines). More on this in a section below. The interpretation of VR Dilation VR dysfunction is usually a prerequisite for submassive or massive PE. Alternatively, the lack of VR dilation suggests that hemodynamic instability may be caused by another problem (e.g. small PE plus septic shock). When possible, it should be compared to file echocardiograms or studs. This can help differentiate chronic ventricular insufficiency vs. acute right. Chronic right ventricular dysfunction is common in patients with COPD or obesity hypoventilation syndrome, so this should not be misinterpreted as evidence of a (sub)massive PE. PE exists in a spectrum of severity of the disease. Therefore, the divisions are somewhat arbitrary. However, it is useful to divide pe into approximately five categories: low risk PE: Patients with the lowest to die. Some may be able to be discharged home (a topic beyond the scope of this chapter). Low-risk submassive PE: Patients with VR dilation, but who are at low risk of dying and do not require intensive care. Intensive. Submassive PE: Hemodynamically stable patients who, however, have raised mortality. They deserve admission to the ICU and consideration for advanced therapies. Massive non-crashed PE: Patients with hypotension who stabilize well in low-dose vasopressant. These patients need admission to the ICU and advanced therapies. Massive PE crashes: Patients with hypotension and persistent characteristics of instability, who are at increased risk of immediate death. patients who defy the immediate stratification of risk Some patients do not fit perfectly into one of the above categories. This is most clinically relevant for patients with submassive PE who are sitting on the borderline between low-risk submassive PE versus high-risk submassive PE. As with all things, clinical judgment is required (potentially considering additional features such as ability to effort, neutrophilic to the ratio of lymphocytes, and the lower burden of limb clots, as discussed further below ↓). For patients who are actually on the low submassive vs. high-risk submassive PE limit, consider: Admission to intensive care. Follow-up of vital signs series, lactate level, and troponin level. If patients remain stable with low levels of troponin and lactate, then they can be classified into low-risk submassive PE. Alternatively, evidence of hemodynamic instability or increased biomarkers can push patients into a high-risk or even massive submassive PE category. Large persistent DVT neutrophil/lymphocyte ratio (NLR) Neutrophilic/lymphocyte ratio is a measure of hidden physiological stress (because endogenous cortisol will increase neutrophil count and reduce the count of lymphocytes, thereby increasing the proportion). The meta-analysis suggests that elevated NLR may be an even stronger prognostic indication than troponin, as shown in the figure below (28541022, 25976228, 29508224). Studies have used different NLR snippets, creating a gray area. Based on the available data, NLR can be interpreted in the sharp PE context as follows: NLR <5.5 suggests= low= mortality= risk= (~2.7%)= nlr= 5.5-9.2 = is= a= grey= zone= (nlr= in= this= range= is= nonspecific= and= adds= no= useful= information)= nlr=>9.2 suggests a high mortality risk (~26%) NLR can be useful as an early indicator of severe PE, because it will often be available early (for example, before lactate or troponin levels have been sorted). Warning: NLR can be elevated for any cause of physiological stress. Therefore, this test will be predictive of PE-related mortality only in patients with isolated PE (no other active medical problems). This is a bit like dairy, as it is a global reflection of physiological stress. foot challenge test Some patients will report pre-syncope or syncope, or breathlessness with an effort If the story is unclear, this can be clarified somewhat by asking the patient to walk (with assistance, to make sure against the fall). The key parameter to follow is the way the patient looks and feels when walking. If patients become (pre)syncopapic or severely dyspneic with a minimum </5.5> </5.5> this implies a significant strain on the right ventricle with low physiological reserve. It can be used serially to evaluate the patient's evolution over time and responsiveness to various therapies. The main challenge in the prognosis is the integration of a lot of information in a non-redundant way. If the list of factors to consider is too long, then we will miss out on it. Brain natriuretic peptide (BNP) or NT-BNP This is used in some prognostic systems, but seems to be abandoning the favor. BNP does not distinguish between the failure of the right or left ventricle. In addition, NT-BNP rises in kidney dysfunction. In general, this makes the test not specific to the diagnosis of acute right ventricular failure. Inclusion can cause patients with chronic heart failure to be incorrectly classified. BOVA Score This is a four-component risk stratification system for PE. It's good, but not perfect. The bova score does not ensure that instability is due to pulmonary embolism (specifically, it does not require VR dysfunction). Patients with mild tachycardia (HR > 110 b/m) and high troponin would be classified as intermediate risk (7% risk of PE-related mortality), even with a completely normal right ventricle. This does not make much sense, as it would tend to suggest an alternative etiology of patient instability. Pesi (Pulmonary Embolism Severity Index) score and simplified PESI score (SESI score) These are designed to predict 30-day cause mortality. This frankly is not what we need to know when stratifying the risk of a PE patient (we need to know the short-term risk of PE-related hemodynamic collapse). As a tool for predicting subacuda mortality, pesi focuses excessively on the patient's basic epidemiological characteristics (rather than the acute hemodynamic state of the patient). Elderly patients with many comorbidities will be classified as high risk even if they have a small pulmonary embolism. Patients with high-risk submassive PE may (incorrectly) receive a low-risk heavy score. This is a well known problem with scoring. According to esc 2019 guidelines, signs of VR dysfunction or elevated levels of cardiac biomarker may be present, despite a calculated PESI of I-II or a sPESi of 0. Until the implications of these discrepancies for PE management are fully understood, these patients must be classified in the intermediate risk category. not getting a CT is a common mistake in (sub)massive CT management are commonly avoided because of fears that they may cause renal failure of contrast nephropathy. Venous contrast nephropathy for CT scans probably does not exist. If you really believe that the patient may have a submassive or massive PE and the patient has kidney dysfunction, A TAC STAT. The risk of dying from PE is more real and greater than any theoretical risk that may exist from contrast IV. empirical lysis in patients with rugged PE, massive From time to time, it will be advisable to proceed to thrombolysis in a patient with massive PE that is too unstable to be transported to the CT scanner. This should be done only if there is an extremely high suspicion of massive PE, for example: i) Bedside ultrasound shows dilation DVT, VR, and all other clinical characteristics that are consistent with pe. ii) The patient is presented in severe shock after discharge at home from orthopedic surgery. Echocardiography and EKG show RV dilation with tension, and there is no evidence of a diagnosis of competition. Be careful that empirical thrombolysis without CT can create an extremely confusing image if the patient does not improve or begins to bleed (because the initial diagnosis is unclear, and accumulates more complexity in this). Below is the physiology of sudden death due to PE. This is a vicious cycle, which can quickly spiral out of control. The cyclical nature of this explains why patients may be stable one minute, but crash the next minute. The rest of this chapter focuses on how to interrupt this process. avoid unnecessary lines and ABGs Patients with massive PE will often require thrombolysis. Minor vascular trauma that occurs when placing an arterial or venous line can become a real problem after giving thrombolysis. Therefore, unnecessary lines or ABG sticks should be avoided. Peripheral lines are fine for short-term use of vasopressors (especially epinephrine). An ABG or VBG is very unlikely to change management. If the lines are to be placed, they should be inserted with extreme care by the most experienced operator with extreme care. For example, a central line should ideally be placed at the first entrance of the ship (instead of going through the ship and then backing off, injuring the ship's back wall in the process). avoid intubation Intubation often precipitates cardiac arrest for several reasons: Sedants can drop blood pressure. Positive pressure inside the chest reduces preload. Over-distension of the lungs can compress pulmonary capillary, increasing pulmonary vascular resistance. Whenever possible, intubation should be avoided or delayed: High-flow nasal cannula can be used for dyspneic or hypoxic patients to prevent or delay intubation. This can be combined with inhaled pulmonary vasodilators (more on this below). If thrombolysis is ordered, try to give first to thrombolysis and then intuit later (or ideally never, if the patient responds to thrombolysis). Unless the patient has lost their mental state or developed respiratory exhaustion, intubation will not be beneficial. If intubation cannot be avoided, the following measures may reduce the risk of cardiac arrest: Before intubation, try to increase systolic blood pressure to ~130-140 mm, usually with an epinephrine infusion. This will give you a margin of error to work with, pressure drops after intubation. Be prepared with epinephrine thrust dose to support blood pressure after intubation. Have a low threshold to use hypotension or worsening of bradycardia. Consider getting inhaled pulmonary vasopressants to the bedside and ready to be donated through the ventilator circuit as soon as the patient is intubated. Administration of a dose of milrinone through the endotracheal tube can also be used, if this is available. Use meticulous pre-oxygenation and apnea oxygenation, along with the intubation of the most experienced operator present. These patients will respond very badly to hypoxyma or hypercarbia. Use sedants that are hemodynamically stable (e.g. ketamine). After intubation, do not overdesensist the lungs (this will increase pulmonary vascular resistance). Avoid excessive ventilation of the bag, which will cause excessive intratoracic pressures. Pay close attention to hemodynamics and oxygenation of the patient in the first 10 minutes after intubation, as this is when they are most likely to stop. The point of greatest risk could be ~5 minutes after intubation, which is often when people stop paying a lot of attention to the patient. Patients can take some time to slide into the death spiral. The ideal way to achieve this is Weingart's hemodynamically neutral intubation, but this is somewhat involved and may not be possible in many scenarios. ideal fluid balance in massive PE? Excessive preloading can aggravate VR dilation, which impairs heart function. The vast majority of patients dying of massive PE will already have high filling pressures (due to the backing of blood behind a failing right ventricle). The potential risk of fluid generally outweighs the potential benefit in these patients. general approach Evaluate with ultrasound. If there is clear evidence of hypovolemia (e.g. small IVC with respirofasic variation), give liquid sensiblely and in small amounts. Note that a small IVC rarely or almost should never occur in massive pe. This could conceivably occur if the patient runs out of volume and also has a massive PE. So, if you see a small IVC, think carefully about whether the patient really has a massive PE. If the IVC is dilated, do not give liquid. Note that mass PE is generally not a depleted state of fluid, so most patients will not benefit from fluid. If the patient has already received a substantial volume of fluid, consider diuresis. Epinephrine is usually the first line agent Epinephrine may be the frontline agent here, for various reasons (8325096): (a) beta-agonist activity of epinephrine can cause pulmonary vasodilation. (b) Massive PE causes death due to failure of the right ventricle (it is fundamentally a form of cardiogenic shock). Beta-angonist stimulation can improve the contractility of the right ventricle, thus improving cardiac production. (c) The most common final terminal route pulmonary embolism is often a Brady-Asystolic arrest. The positive crootropic effects of epinephrine can act to block this event. The establishment of adequate average blood pressure (e.g. > 65 mm) will help ensure adequate perfusion of the coronary artery and thus support the right ventricular function. There is no specific maximal dose of epinephrine for use in the patient with massive pulmonary embolism. High doses may be necessary. Vasopressin can be used as a second-line vasopressin agent causing systemic vasoconstriction, while at the same time causing pulmonary vasodilation. Beneficial effects on pulmonary vasculature make vasopressin a good option in pulmonary hypertension. The typical dose range could be similar to a dose of sepsis (e.g. 0-0.06 U/min) (27483065). Vasopressin is usually used as a second-line agent because it is not tremendously powerful and is difficult to titrate (with a half-life of ~20 minutes, its start and displacement are slow). why inhaled pulmonary vasodilators can be useful: It can improve oxygenation by improving ventilation-perfusion matching. It can improve hemodynamics (postload-reduction of the right ventricle compensates for obstruction due to clot). Much of the hemodynamic deterioration due to PE is not due to the clot itself, but to the pulmonary vasoconstrictors that are released in response to the clot. Pulmonary vasodilators are a rational approach to combating this. Evident basis for pulmonary vasodilators The iNOPE trial randomized 76 patients with submassive PE in placebo vs. nitric oxide inhaled at 50 ppm for 24 hours. Inhaled nitric oxide increased the likelihood of having a normal-sized right ventricle. It was well tolerated without any adverse events (more discussion of this study here). choice of nitric oxide vs epoprostanol There is no strong evidence to compare one agent with the other. In general, available evidence generally does not find major differences between the two agents. In practice, the best agent is the one who can get to the patient's bedside faster. Both agents can be given to unstubated patients or intubated patients. If you do not have access to pulmonary vasodilators, please note that oxygen causes pulmonary vasodilation as well. High fio2 oxygen is the pulmonary vasodilator of a poor person. Nitric oxide and epoprostanol act through different mechanisms, so they can be used together in attempts to target synergy pulmonary vasodilation. bottom on heparin Heparin prevents additional clots from forming, but does not break down the existing clot. Heparin began to be used before the era of evidence-based medicine. Consequently, there is essentially no evidence of high quality regarding the use of heparin in pe. Retrospective studies from time to intervention suggest that early heparin has a great benefit to mortality. These studies are probably flawed and are generally extremely dubious. For patients with (sub)massive PE who are receiving tPA or who will immediately receive tPA, heparin the risk of bleeding without providing any proven benefit. Nofractioned heparin is preferred in sub(massive) PE For most pulmonary emboli, low molecular weight heparin has been shown to have a lower risk of bleeding. Therefore, low heparin is usually the preferred form of heparin to embol pulmonary low risk. For (sub)massive PE, nofractioned heparin is generally preferred for the following reasons (31185730): (a)

It can be stopped if the patient begins bleeding. (b) It can be stopped or lowered in anticipation of thrombolysis or procedures. Anticoagulation approach in (sub)massive PE Below is my preferred strategy for anticoagulation. (back to content) The use of thrombolysis for massive PE is widely accepted as the level of care. This has been shown to reduce pe mortality and recurrence compared to anticoagulation alone (30325344, 15262836, 22325236). The controversial bit is the use of thrombolysis for submassive PE, which is explored further. For a time, it was believed that thrombolysis would reduce the risk of chronic thromboembolic pulmonary hypertension and thus improve long-term functional extremes. The long-term results of the Peitho trial convincingly rejected this (28335835). This greatly simplifies things. Currently the main reason for using thrombolysis is to reduce the risk of cardiac arrest. Unfortunately, evidence on thrombolysis remains murky for the following reasons: (1) Studies usually include a heterogeneous group of patients with a range of severity and age of PE. This tends to make large studios have a neutral result. (2) The absolute magnitude of the benefit is relatively small, which causes many studies and meta-analysis to be underpowered. (3) Studies often overlap thrombolysis and anticoagulation of heparin in a dangerous manner, with subsequent attribution of bleeding events to the thrombolytic agent. (4) Studies involve different thrombolystic drugs and in different doses, which limits the generalizability between studies. For the above reasons, there is no large, multi-center RCT that has unequivocally demonstrated the benefit of thrombolysis in submassive PE. Meta-analysis has suggested that thrombolysis reduces total cause mortality in submassive PE, but this finding is not robust; see figure below (29175415; 24938564). In order to build a logical argument about the use of thrombolysis in submassive PE, we need to extrapolate the results of numerous studies as below. Principle #1: thrombolysis reduces the risk of thrombolysis cardiovascular collapse has been shown in several studies to cause an immediate reduction in pulmonary vascular resistance and, therefore, an immediate improvement in correct ventricular function. This relieves VR voltage, and reduces the risk of acute VR failure. Two multi-center RCT have shown that thrombolysis decreases the risk of hemodynamic impairment (MAPPET and PEITHO). In general, numerous studies support the concept that thrombolysis will greatly reduce the likelihood of cardiovascular collapse (by ~50%)(30560579). #2: thrombolysis with alteplasa is safer than is normally believed that alteplasa carries a high risk of intracranial bleeding. However, is not supported by high quality prospective tests. The risk of intracranial bleeding due to alteplasia in potential RCTs is shown in the table below. Available studies are not very powerful in clearly defining the risk of intracranial bleeding, but it seems to be low. Particularly for small dose regimens of alteplasia (e.g. 50 mg), the risk is likely <1%. this= risk= may= be= minimized= by= avoiding= simultaneous= exposure= to= alteplase= and= heparin= (more= on= this= below).= principle= #3:= complete= resolution= of= clot= isn't= necessary= the= goal= of= lytic= therapy= isn't = to= normalize= the= pulmonary = pressures,= but= rather= merely= to= cut= back= pressure= sufficiently= to= prevent= sudden= cardiac= death.= a= moderate= reduction= in= pulmonary= pressure= may= be= achievable= with= a= lower= dose= of= thrombolytic= than= has= been= used= traditionally= (e.g.= 12-50= mg= alteplase).= this= may= carry= a= lower= risk= of= hemorrhage,= thereby= improving= the= overall= risk/benefit= ratio.= risk-benefit= calculus= let's = approximate= the= risk= of= systemic= thrombolysis= as= a= 1%= risk= of = intracranial= hemorrhage.= this= is= probably= higher= than= the= true= risk= (especially= if= reduced= doses= are= used= with= avoidance= of= simultaneous= heparin= use).= if= a= patient= has= a=>5% risk of cardiac arrest due to PE , then should benefit from thrombolysis: Added risk of intracranial bleeding = 1% Reduction of heart arrest rate = (>5%)(>50%) = >2.5% The exact numbers here are debatable. However, in general, a patient with real risk of dying of PE (for example, with a short-term mortality of >5%) it is likely to benefit from thrombolysis. Of course, the benefit is better evaluated based on the patient per patient, weighing the risk of death from PE against the risk of bleeding due to thrombolysis. contraindications to thrombolysis: a first start reviewing patient medications, history, and coagulation laboratories. Contraindications are traditionally divided into relative and absolute contraindications, but this must be taken into clinical context. For example, neoplasm of the NC appears as an absolute contraindication, but there are reports of cases of these patients receiving thrombolysis. If the patient is actively dying of PE and there are no good options, it may be necessary to use thrombolysis despite the presence of an absolute contraindication. Note that some absolute contraindications to PE thrombolysis (e.g. ischemic stroke) are actually indications for thrombolysis in other situations! So these are not truly absolute contraindications. list of contraindication of PE Brain/hemorrhagic CVA spinal pathology (absolute) ischemic CVA (absolute if within 3 months; otherwise relative) Known vascular disease, for example, arteriovenous (absolute) Brain or spinal surgery (absolute if recent) NC tumor (relative) Diabetic retinopathy (relative) Trauma/surgery/recent head trauma procedure with fracture or brain injury within three weeks (absolute). Minor head trauma due to syncope is not necessarily a barrier to fibrinolysis (AHA/ ACC 2011). Major </1%.> </1%.> surgery within 2-3 weeks (relative) Recent puncture of non-compressible glass (relative) History of severe active bleeding bleeding, excluding the menses (absolute) Recent internal bleeding within 4 weeks (relative) Known coagulation platelet studies < 100,000= (relative)= warfarin= use= with= inr=> 1.7 (relative) Fibrinogen <150 mg/dl= (relative;= usually= don't= delay= treatment= in= massive= pe= if= fibrinogen= is= unknown)= anticoagulants= oral = anticoagulation= (relative)= multiple= anticoagulants,= e.g.= anti-platelet= agents= (relative)= htn= history= of= chronic,= severe,= poorly= controlled= htn= (relative)= blood= pressure= on= presentation=>180 systolic or >110 diastolic (relative) Age >75 years (relative) Dementia (relative) Specific situations Pregnancy or first postpartum week (relative) Infectious endocarditis (relative) Advanced (relative) Advanced Cirrhosis Tool PE-CH to predict the risk of intracranial bleeding during PE thrombolysis (27882375). This was generated and validated using a large data set of community hospitals in the United States. Counting points for the patient: Peripheral vascular disease = 1 point Age > 65YO = 1 point Before stroke with residual deficit = 5 points Previous myocardial infarction = 1 point Risk of intracranial bleeding after systemic thrombolysis: 0 points = 1.2% 1 point = 2.9% 2 points = 3.4% 5 points or more = 18% This was based on with attribution of all intracranial bleeding to thrombolysis (as opposed to heparin, or other causes). As such, you will inevitably overesas the risk of intracranial bleeding caused by thrombolysis. However, this can remain a reasonable tool for measuring roughly relative risk. The key point is that patients with vascular disease anywhere in their body (e.g. coronary arteries, peripheral arteries) are at risk of hidden cerebrovascular disease that will lead to an increased risk of intracranial bleeding. Thrombolysis for PE is used much less often than thrombolysis for ischemic stroke or myocardial infarction. This has led to many of our practices regarding thrombolysis to be borrowed from thrombolysis for stroke or for myocardial infarction. For example, the list of above absolute and relative contraindications seems to be adapted from the literature on myocardial infarction and stroke. One aspect of thrombolysis borrowed from IM and stroke literature seems to be the dose. Full-dose alteplasa for pulmonary embolism (100 mg of alteplase) is very similar to the regimens used for myocardial infarction (maximum dose 100 mg) and stroke (maximum dose 90 mg). That was probably a big mistake. why PE requires lower doses of alteplasia than IM or stroke: 100% of the alteplasa-infused dose will go to the pulmonary arteries (unlike, say, ~ blood flow that goes to the coronary arteries in myocardial infarction). The half-life of the alteplasa is ~4 minutes, which means that each alteplase molecule will pass through the lungs about five times. </150> </150> pe occlusion is due to the formation of clots. Compare this, for example, with a coronary artery that can be partially occlusive due to a plaque with a moderate contribution due to acute clot formation. The higher the amount of occlusion of the ship that is due to the clot, the greater the effectiveness of thrombolysis (and therefore a lower dose is required). We don't need a complete clot resolution – all that is required to improve patient outcomes is partial improvement. The immediate opening of some pulmonary arteries (while other pulmonary arteries remain occluded) may be suitable to produce an excellent clinical outcome. evidence that surprisingly low doses of alteplase are effective: The literature contains numerous case reports and case series describing the use of extremely low doses of alteplase (e.g. 4 mg) in PE used for patients with contraindication at higher doses. These reports are not definitive, but suggest that small doses of alteplasa may be much more effective than we believe, especially for fresh thrombins (21127275). The OPTALYSE PE trial was a prospective trial comparing different alteplase regimens administered through catheter-led thrombolysis. There was no apparent difference in efficacy between doses of ~8 mg and ~24 mg. This suggests that low doses of alteplasa may be much more effective than we realize (more discussion of this study here). Aykan 2014 published a series of cases describing the use of alteplase infusions of 25 mg for 6 hours in high-risk PE patients with contraindications to higher doses of thrombolysis. This relatively low dose of altheplasia caused a dramatic drop in systolic pressure of the pulmonary artery (from 57 mm to 34 mm) – essentially identical to the effects that could be expected of 50-100 mg of alteplasia. The dose was well tolerated, without severe hemorrhagial complications (despite use in patients at increased risk of bleeding). This, again, indicates that low doses of alteplasia may be entirely suitable to cause clinical improvement. Thrombolysis full dose 100 mg iv alteplasa (tPA) for 2 hours has traditionally been considered as full dose thrombolysis, for use in massive pulmonary embolism. This dose was selected arbitrarily. There is no evidence to support the use of this dose, compared to a lower dose. 100 mg is probably an excessive dose for almost all patients. For patients with massive PE crashing, the initial ~20 mg can be given as an IV thrust (with the remaining medication infused for two hours). Thrombolysis half dose Typical regimen based on the MOPETT trial: Dose of alteplase = 0.5 mg/kg up to a maximum dose of 50 mg (23102885). First 10 mg infused as a bolus, followed by the rest for 2 hours. 50 mg of alteplasa has been shown to have an identical efficacy in with 100 mg of alteplasa, with fewer complications of bleeding (lower figure)(19741062). These same results have also been found in other studies and meta-analysis (30068253). Thrombolysis quarter-dose (25 mg alteplasty) Ideally of alteplasa in PE remains unknown. As discussed above, the optimal dose is probably lower than generally used (for example, perhaps in the range of 15-40 mg). The most evidence-based approach to using quarter-dose thrombolysis is to provide this as a slow infusion (e.g. 1 mg/hour). This is identical to the use of altheplasia in catheter-led thrombolysis by PE or DVT (except that the drug is inflowed into a peripheral vein). The safety of this regime has been established by dozens of studies over many years, with a risk of intracranial bleeding at the height of a standard infusion of heparin. Its effectiveness in PE is less well established in literature, but it seems to work. This is an alternative to catheter-led thrombolysis, depending on availability and local rules. Below is a protocol for this. An essential component of this strategy is the close monitoring of bleeding or excessive coagulopathy, with the ability to immediately stop alteplasa infusion if necessary. More discussion of this strategy here. Fallacy of using fixed doses of alteplase Almost all studies of thrombolysis in PE are based on the use of specific dosing regimens in an entire population of patients. However, this strategy is deeply flawed because the balance of fibrinolysis vs. fibrin generation is extremely complex and variable among patients. Therefore, different patients can respond to the same dose of thrombolytic in dramatically different ways. For a patient who is not actively dying, the most sensible approach might be to provide tittered doses of fibrinolytic, while closely monitoring coagulation parameters (especially fibrinogen). There are approximately two ways to do this: (a) Administration of fibrinolytic as a continuous slow infusion, with monitoring of coagulation parameters over time (commonly done in interventional radiology and also described immediately above). (b) Intermittent administration of reduced doses of thrombolytic (eg, 10-25 mg of alteplase) with reassessment of clinical and coagulation parameters before administration of each dose. How to coordinate the use of heparin and thrombolysis remains a largely evidence-free area. The available evidence on this is explored in detail in a previous blog here. before thrombolysis: ideally stop heparin and allow it to wear out of heparin anticoagulation and thrombolysis can be performed simultaneously, but this is generally not preferred. The MOPPETT trial combines full dose anticoagulation with enoxaparin (1 mg / kg q12hr) with mid-dose tPA. The PEITHO trial combined full-dose anticoagulation with heparin and thrombolysis (so they probably had a very high rate of intracranial bleeding). Therefore, a patient who anticoagulate (e.g. with enoxaparin) and develops hemodynamic instability can receive thrombolysis. For a patient undergoing systemic thrombolysis, heparin increases the risk of bleeding without providing any proven additional benefit. Ideally, the heparin will stop and will be allowed to clarify patient before systemic thrombolysis. This may be possible for hemodynamically stable patients with submassive pulmonary embolism, but not for patients with massive pulmonary embolism. after thrombolysis: when to resume heparin? Although tPA has a short half-life, it causes several persistent abnormalities in the clotting system, including: (1) Reduced levels of fibrinogen. (2) Fibrinogen degradation coagulopathy (degraded pieces of fibrinogen actually exert anticoagulant effects!). (3) Reduced platelet function (due to the cleavage of glycoprotein Ib receptors on the platelet surface) (30474416). The traditional approach has been to resume heparin (without bolus) when the PTT is below 1.5-2 times normal. Checking a level of fibrinogen before heparin resumption makes sense, as tPA can have unpredictable effects on fibrinogen levels. It may be reasonable to avoid resuming heparin infusion until fibrinogen is over ~100-150 mg/dL. In general, if the patient has a favorable response to thrombolysis (clinical improvement, weaning of vasopressors), then waiting longer before resumption of heparin can increase safety and reduce the likelihood of bleeding. illustration of what happens when heparin and alteplasa are combined suboptimally: As shown in the following table, tenectplasa has been associated with a higher bleeding rate than alteplasa (25457585): The reason why tenectplasa has been associated with more bleeding is unclear. It can be related to a dosage problem, in which studies have generally used full dose tenectplase (i.e. the same dose used for STEMI thrombolysis). It could relate to the use of simultaneous bolusas of tenectplasa and heparin in the peitho trial (which is a formula for disaster). Based on the above data and generally a greater breadth of experience using alteplasa, the first line lite choice for PE is currently alteplase. If the alteplasa is not available, tenecteplase could certainly be used for massive PE. Tenectplasty is a little easier to reconstitute, so tenectplasty may have an advantage in PE-induced cardiac arrest if it were faster to access it. Catheter-led thrombolysis This involves placing bilateral catheters in the pulmonary arteries to directly infuse tPA in close proximity to the clot. (Casual patients may have unilateral clot, but in most patients there is bilateral clot requiring bilateral catheter.) There is little theoretical or obvious support for why catheter-led thrombolysis should be higher than the administration of an identical dose of tPA through peripheral circulation (all peripherally infused TPA will be transported directly to lung circulation). All available studies have funded by pharma. These studies compared catheter-led thrombolysis with anticoagulation with heparin (which is a straw comparator) or conducted a study of an arm without a comparator group at all. The lack of willingness of the pharmaceutical company to finance a comparison of catheter-led thrombolysis versus catheters is visible (24226805, 26315743). An RCT is currently underway to finally try to clarify whether catheter-led thrombolysis is better than the administration of an equal dose of tPA through peripheral vein (NCT03581877). Some catheters use ultrasonic energy in efforts to break the clot. Available data suggest that ultrasound energy has no benefits. Overall, the addition of ultrasonication seems to be a useless luxury added by device companies in efforts to market an expensive catheter (25856269, 27630267, 28827014, 25593121, 26993702, 30915914, 30915912). The main benefit of catheter-led thrombolysis is probably derived only from the use of low-dose thrombolysis. This is a safe and effective treatment that can be very beneficial – especially in a hospital that is uncomfortable with the use of low-dose peripheral thrombolysis (a common problem). Traditionally, the most common dose of tPA has been 0.5-1 mg/hour per catheter for a total dose of 12-24 mg delivered over a 24-hour period (31185730). The recent OPTALYSE trial suggested that tPA may be more effective than previously believed, so the optimal dose could be ~8-12 mg total (30025734). The optimal dose of heparin nofractioned during catheter-led thrombolysis is unknown. The safest approach could be a fixed low-dose infusion at ~500-1,000 units/hour (31185730). Amazing immediate results with @InariMedical. Pressure reduction of 12 mmHg and immediate symptomatic improvement @JeffersonRads. Difficult to deny immediate response and lack of risk of TPA-related bleeding. TBD for significant long-term benefit @akhileshsistaMD pic.twitter.com/tpxFaD0fNT — Ronald Winokur, MD, FSIR, RPVI (@RonaldWinokurMD) September 4, 2019 percutaneous mechanical thrombocytomy The true benefit of interventional radiology probably lies in the extraction of physical clots. Potential indications: Patients with submassive or massive high-risk PE with contraindication to thrombolysis. Patients in whom thrombolysis could not be effective. The evidence base for the extraction of clots is relatively scarce. In addition, it is a procedure dependent on the operator, so the tests may not necessarily be generalizable from one center to another center. Results are likely to be higher in high volume centers. There are several devices available, as follows: Inari FlowTriever system device designed to remove clot from lung arteries (see video below). FLARE Study: Single-arm trial involving 106 patients with submassive PE treated with FlowTriever. A substantial reduction in the VR/LV ratio was achieved (from 1.56 to 1.15 for 48 hours, on average). Almost all patients did not receive any thrombotics, so was a true study of mechanical intervention. The rate of serious adverse events was low, at 4% (31072507). More evidence is needed to see how this device will work outside the confines of a clinical trial. However, the available evidence looks very promising at this stage. Stage. Indigo embolectomy system currently supported by case reports, with a possible multi-center trial in progress (NCT03218566). AngioVac Large (22F) catheter that removes emboli through a centrifugal pump with blood return (similar to cardiopulmonary bypass). Best for clots in the lower vein cava or right ventricle (access to the pulmonary artery is difficult and can increase the complication rate)(31185730). AngioJet device designed to break the clot inside the vasculature. He has won a black box warning from the FDA causing numerous adverse events (including bradycardia, massive hemoptysis and kidney failure). The available evidence does not support its use. For many years, surgical thrombocytomy was thought to be excessively dangerous and generally unhelpful. However, this procedure has made a resurgence over the past decade. Currently the mortality rate of the procedure is approximately 10%, which can be reasonable in selected patients at a very high risk of death from PE (31185730, 28942971, 27373187). potential indication for Clot-in-transit surgical thrombocytomy found through an oval patent hole (PFO). This situation carries a risk of immediate stroke if the clot breaks and parts of it enter the systemic circulation. Therefore, surgery can be a first-line intervention in this rare scenario. Massive PE in a patient with absolute contraindication to thrombolysis. Massive PE with failure of other interventions (e.g. lyrical failure). ~ 10% of clots will not respond to thrombolysis (perhaps because they are chronic and have undergone organization). Surgical thrombocytomy vs. extraction of clots of interventional radiology There is currently no evidence of high level comparing these modalities. Advances in the incarnation of the catheter (e.g. the Inari Flowtriever system) could make interventional radiology approaches superior in many cases. However, further study is needed. (sub)massive PE patients can be excellent candidates for VA-ECMO if this therapy is available. Unless patients have suffered a severe anoxic brain injury (due to cardiac arrest) or have other active problems, they usually need to improve if they can be supported. The role of VA-ECMO is largely defined by available resources, with some potential uses listed below. Possible indications for ECMO may include the following: Massive PE in a patient with absolute contraindication to thrombolysis. Stabilization of a patient with massive PE before intubation. Patient with massive PE and persistent instability despite thrombolysis (lytic insuflication). Potential roles for VA ECMO may include: Bridge to the efficacy of anticoagulation: Over time, patients generally degrade the clot by account (with systemic anticoagulation to prevent additional thrombosis). Therefore, ECMO can only be enough to support the patient for several days to allow natural thrombolysis. Bridge to controlled thrombolysis: ECMO could be used to support a patient while while Gradual thrombolysis (eg, 1-2 mg / hour of infusion tPA, either systematically or by catheter-led analysis). Bridge to intervention: ECMO could be used as a bridge to other definitive therapies (e.g. catheter-led thrombolysis or cardiothoracic surgery). There is no high-level evidence regarding VA-ECMO in PE, nor is this evidence likely to emerge in the near future (given the rarity of this situation). The main limitation of ecmo is that it is only available in a limited number of centers. Possible clinical effects of an IVC filter include: It could intercept clots that travel to the lungs (thus avoiding pulmonary embolism). It could increase blood stasis in the legs (thereby increasing the risk of deep vein thrombosis). It could become thrombo, leading to blood occlusion in the lower vein cava. It can cause a procedural complication (e.g. filter wrap or bleeding). Penetration of the cava vein wall occurs in 19% of procedures! (26169756) From a theoretical point of view, an IVC filter is a bit of a commode. It can cause both potential benefit and potential harm. There is no good obvious support for the IVC filter (previously discussed here). The most relevant study regarding submassive PE is prepic-2, which showed that the use of IVC in patients with large PE in anticoagulation caused a tendency towards harm. Traditionally, IVC filters have been used among patients with contraindication to anticoagulation. However, there is precisely zero evidence that IVC filters are beneficial for this situation. The inability to anti-coagulation may increase the risk of Thrombosis of the IVC filter. In general, there is no good evidence that the theoretical benefits of IVC filters outweigh their numerous risks. The placement of thousands of IVC filters over decades is a case study in fear-based medical practice, reinforced by eminence-based guidelines (23552611). That said, placing IVC filters could be reasonable if all of the following criteria are met: Inability to receive anticoagulation. (Sub) Massive PE with low hemodynamic reserve. Known DVT with high load of clots (especially large, free floating, proximal DVT). If an IVC filter is placed, a recoverable filter must be used. This must be deleted in the first available opportunity. Unfortunately, it requires much less courage to insert a DVT filter than to remove it. Consequently, studies consistently show that most recoverable IVC filters are not recovered in fact (28123984). The implantation of prolonged filters increases the risk of recovery failure, filter migration, IVC perforation, filter embolization or filter thrombosis (31185730). Pe hemoptysis is the result of lung infarctive. This usually occurs a little later in the natural course of PE (after the clot break and the fragments migrate distally). As such, it is somewhat unusual for a patient with submassive or massive PE to have hemoptysis. Hemoptysis is usually seen during a recovery phase, at which point the patient does not has a high load of central clot. PE hemoptysis reflects necrosis of the lung tissue of the heart attack, which causes bleeding from pulmonary capillary and veins. Since bleeding does not originate from the pulmonary arteries, bleeding is usually lower. It is extremely unusual for a patient to have massive hemoptisis due to PE. As a rule, anticoagulation can continue despite hemoty. Similarly, hemoptysis is only a contraindication relating to thrombolysis. Pe hemoptysis key points is generally lower, and hardly ever life threatening. Hemoptysis should not have a major impact on the treatment strategy for PE. Do not stop anticoagulation due to hemoptysis (unless hemoptysis is unusually risky). Pulmonary embolism is a known cause of ST. elevation. More about PE's EKG manifestations here. In cases of diagnostic uncertainty regarding elevation of ST MI vs PE, the best approach may be immediate bedside echocardiography. ST IM elevation should cause regional wall movement anomalies involving the left ventricle and dysfunction of the left ventricle. Massive pe will cause VR dilation and usually a little full left ventricle (which is vigorously contracting). Key points If a patient with known submassive/massive PE develops st elevation, this is probably due to pe itself. Treatment should generally focus on PE management. Not making the mistake of assuming that all ST-elevated patients require cardiac catheterization – in the context of known (sub)massive PE, sending the patient for cardiac catheterization would generally be a reckless maneuver. Prominent Eustochia valve can be confused with the right adphone mass, esp when there is a clinical presentation to support it. #echofirst #POCUS #cardiotwitter pic.twitter.com/tKzEvKn9Nd — Ivan Stankovic, MD, PhD (@Ivan_Echocardio) April 4, 2018 diagnosis of clot in transit: exercise caution There are many things that can mimic the clot in transit within the right ventricle (e.g. Eustacian valves or prominent trabeculations of the right ventricular moderator band). A clinically significant clot in transit is generally quite unmistakable (as a large, thick, highly moving structure such as snake). So, if you're not sure about whether there's a clot in transit, be suspicious about whether it's a real finding and seek expert advice. Avoid assuming that any mobile structure of the right ventricle is a clot in transit. The clot in transit can be broken down into approximately three different entities. Confusion arises because they often come together in one group. Level I hole in traffic Definition: Small clot in transit. This may look similar to a vegetation of endocarditis, such as a small structure attached to the tricuspid valve. This is often a somewhat incidental finding in a which is otherwise doing well. The importance of a small clot in transit is frankly unclear. This probably increases the risk of deterioration somewhat, but not tremendously. I shouldn't have enormous implications for treatment. Level II hole in traffic Definition: Large, mobile, snake clot in transit. This has a rather unmistakable and obvious appearance in echocardiography. A large clot in transit poses a clear and present danger to lung circulation as it is likely to break at some point in the future. This will generally move the patient's severity classification by a class (for example, a patient with a low-risk submassive PE found to have a large clot in transit would be classified as having a high-risk submassive PE). Treatment is similar to pulmonary embolism in general (with increased severity classification taking into account). Systemic thrombolysis is often suitable if there are no contraindications. Retrospective studies suggest improved survival among patients treated with systemic thrombolysis (31185730) Patients with contraindications to thrombolysis could benefit from the extraction of IR clots. Level III clot in transit Definition: Clot-in-transit is encased through an oval patent hole (PFO). This is essentially a paradoxical-embolism-in-transit (clot in the process of sliding the venous system into arterial circulation). This is a huge problem, because it poses a threat of arterial embolization (which could cause a stroke). Thrombolysis is relatively contraindicated in this situation, to avoid causing the clot to break inside the arterial system and precipitate a stroke. Optimal treatment will often involve cardiothoracic surgery to remove it directly. Thrombus is going through the courtesy of PFO- Vk Van pic.twitter.com/Qz9Zu5uddr — kazi ferdous (@fazalabul) August 31, 2019 differential diagnosis: the causes of refractory hyposchemia at ~100% FiO2 Refractory Hypoxmia always reflects some kind of shunt. The differential diagnosis here is quite short. (1) Detour from right to left blood through an oval patent hole (PFO) or atrial septal defect. Pe causes an elevation of the pressures on the right. This causes the right-to-left shunning of deoxygenated blood. (2) Another co-existing lung process (e.g. pneumonia, plugged mucus, or pneumothorax). Cardiopulmonary ultrasound assessment with bedside bubble study to evaluate to avoid shunting. Injection of agitated salinity while imagining the heart is the test of choice to evaluate for the escape from right to left. Additional images on the chest (especially if the study of the bubble is negative) – such as chest X-rays and possibly tC chest. 80 years old with Saddle PE and TIA. PFO confirmed with bubble study due to high PASP. What do we do next? pic.twitter.com/6eZegkZdu2 — Katherine Collins MSc FBSE (@The_Echo_Nerd) February 19, 2015 treatment of pe-induced right-to-left escape (1) High-flow nasal Cannulae with 100% FiO2 is the first thing to try. (2) Pulmonary vasodilators can encourage blood to flow through the lungs (thus decreasing the deviant blood fraction). (3) Advanced PE therapies are indicated (e.g. thrombotics or extraction by interventional radiology). Ultimately, any effective treatment of PE will reduce the pressures on the right and decrease the fraction of deviated blood. Note: Intubation generally won't improve oxygenation due to a right-to-left shunt; it can actually make matters worse (by increasing pulmonary vascular resistance, positive intrathracic pressure can simply increase the fraction of deviated blood). Patients can survive and get it right despite the coding of a PE (with > 50%). Some components useful to this: Thrombolysis: Regardless of the patient's contraindications, they should receive thrombolysis (unless immediate ECMO is an option). The dose of alteplasa code that is best supported by the evidence appears to be a 50 mg IV bolus (27422214). However, if 100 mg is available, administration of this whole dose can also be reasonable. Tenecteplase can be faster to mix, so this is another option. Epinephrine: If the patient recovers a pulse after a bolus of epinephrine, consider immediately initiate an infusion of high dose epinephrine (eg, 20 mcg / min, then titrate based on blood pressure). These patients often seem to re-arrest after epinephrine bolus wears off. Limit airway pressures, as discussed above (avoid overagging overagging). Inhaled pulmonary vasodilator – Consider the administration of any pulmonary vasodilator available through the endotracheal tube (eg nitric oxide, epoprostanol, or milrinone). Provide time for thrombolystics to circulate – Consider extended CPR (e.g. 60-90 minutes) to allow thrombolytic time to circulate. 1) Massive PE patient crashing: 2) non-injured patient: risk stratification and bespoke treatment Follow us on iTunes To keep this page small and fast, questions and discussion about this site can be found on another page here. Submassive PE: The basis of a successful approach is the stratification of reflective risk and thorough evaluation of contraindications to thrombolysis. Be careful when combining thrombolysis and heparin, especially heparin boluses (which can produce supraterapèutic levels). If in doubt, being conservative with heparin (heparin prevents a new clot from forming, but has no immediate impact on the patient, so leaving the patient out of heparin for a few hours is probably fine). Massive PE: Avoid volume management unless there is definitive evidence of hypovolemia coexisting. Feel free to start vasopressants as needed to stabilize blood pressure (with epinephrine potentially as a frontline agent). Do not delay thrombolysis if it is an option. Thrombolysis is the only intervention that is supported by evidence to improve in these cases. All other interventions (pressor, inhaled vasodilators, etc.) are intended to stabilize the patient until thrombolysis can be performed. Avoid invasive procedures whenever possible (intubation, arterial or venous lines). Go further: further: far: far: