SAHLGRENSKA ACADEMY

Catheter-directed interventions in patients with high-risk pulmonary embolism and contraindication to systemic thrombolysis

Degree Project in Medicine

Freyr Einarsson

Programme in Medicine

Gothenburg, Sweden 2019

Supervisor: Christian Rylander

Department of Anesthesiology & Intensive Care

Table of contents

Abstract

Background: Intravenous (iv) thrombolysis is the primary treatment for high-risk pulmonary embolism (PE), but in recent years, catheter-directed interventions (CDI) has emerged as an alternative in patients with contraindications to thrombolysis. Although meta-analyses of CDI have reported high rates of clinical success combined with a low risk of serious adverse events, there is considerable variation in techniques, and very few studies are controlled or randomized. The Sahlgrenska University Hospital introduced CDI a few years ago, and there was a need for evaluation of the results of this treatment.

Aims: To evaluate the outcome and effectiveness of the CDI method applied for PE at the Sahlgrenska University Hospital in terms of survival and reduction of right ventricle dilation.

Methods: Retrospective study of patients with high-risk PE and contraindication(s) for systemic thrombolysis. We included patients from July 2013, when CDI was introduced, to December 2018. The control cohort consisted of patients from 2006 to 2013, before CDI was introduced, who fulfilled the inclusion criteria but received either heparin or iv thrombolysis.

Results: Ninety-day survival was 59% in the CDI group (n=22) and 61% in the control group (n=23). In a linear mixed model, with adjustment for timing of pre- and post-treatment imaging, the decrease of right ventricle/left ventricle (RV/LV) ratio was 0.4 units higher per 24 hours in the CDI group (p=0.007).

Conclusions: In this retrospective observational study of patients with high-risk PE and contraindication to thrombolysis, treatment with CDI was as effective as treatment with anticoagulation (or iv thrombolysis) with regards to survival. Moreover, CDI resulted in faster resolution of RV dilation. The latter is to be interpreted with caution since the patients in the CDI group had higher pre-treatment RV/LV ratios.

Key words: high-risk pulmonary embolism, catheter-directed interventions, thrombolysis, anticoagulation, AngioJet.

Background

Pulmonary embolism is the third most common cause of cardiovascular mortality, after coronary artery disease and stroke, and accounts for 5%-10% of in-hospital deaths in western civilizations[1]. The incidence is approximately 50-100 cases per 100 000 individuals and year in the general population, with numbers in the higher interval more often reported in studies on recent data, which is thought to be attributed to the increased use of computed tomography (CT) for diagnosis, as well as an ageing population[2-5].

Acute PE can be divided into three categories based on severity[6]:

Low-risk (non-massive) - Haemodynamically stable.

Intermediate-risk (submassive) - Haemodynamically stable, but with right ventricular (RV) dysfunction, dilation or hypokinesis, at computed tomography (CT) or echocardiography.

High-risk (massive) – At least one of the following: (1) Systolic arterial pressure < 90 mm Hg, (2) a drop in systolic arterial pressure of at least 40 mmHg, for at least 15 min (which is not caused by new onset arrhythmias), or (3) shock, evidenced by (≥1): cool clammy extremities, tissue hypoperfusion/hypoxia, altered level of consciousness, and oliguria.

The classification of PE severity into non-massive – submassive – massive is mainly derived from American literature. As a contrast, European guidelines have divided PE into similar, but slightly different categories: low, intermediate (low/high) and high risk, where low and high are equivalent to non-massive and massive PE respectively. Intermediate risk however is further subcategorized into low and high, with patients with evidence of both RV dysfunction at CT or echocardiography, and elevated cardiac biomarkers, falling into the intermediate-high category, and patients with evidence of only one of these in the intermediate-low category[7].

The degree to which the patient is affected by the condition varies greatly, and is determined by the degree of occlusion in relation to the patient´s physiological reserve, and general health status. The overall mortality rate associated with PE has a wide range as it differs significantly between the categories of severity (Table 1). Patients who remain haemodynamically stable, and are without signs of RV-strain, are often cited to have a mortality rate between 0%-1%, the rate then increases in patients with intermediate-risk PE and high-risk PE, with patients who require cardiopulmonary resuscitation (CPR) showing a mortality rate as high as 57%-77%[2, 8-17].

*Table 1 - Mortality rates stratified by severity and time. RVD = Right ventricular dysfunction (+ with, - without). All-cause deaths except *PE-related deaths. **Cardiogenic shock. ***CPR. ****Without cardiogenic shock or catecholamine support (except for dobutamine ≤5 mg/kg body weight per min). *****Systemic hypotension + shock or catecholamines.*

Table 1	Non-stratified	Low-risk	Normotensive (RVD±)	Intermediate-risk	High-risk
Overall	22%[15]	≤1%[2]		5%-25%[2]	15.2%[15]**** 18%-65%[2] 24.5%[15]***** 25%-30%[2]** 57%[8]*** 65%[15]*****
In-hospital		0%[14] 0%-9.6%[16]		4.3%-4.6%[14]* 8.1%[15] 11.8-23%[16]	65%[15]***
(≤)30 days	9%-11%[17] 10.7%[10]* 11.4%[11]	9.4%[12]		16.3%[12]	37%[9] 77%[9]***
90 days	8.6%-17%[17] 15.3%[11]		14.7%[13] 15.1%[11]		52.4%[13] 58.3%[11]

Clinical Presentation

Pulmonary embolism can produce widely different clinical presentations ranging from asymptomatic to almost instant death, depending on the patient's age and cardiopulmonary health, the degree of vascular obstruction, and the number, size and location of emboli. Symptomatic patients can be divided into three categories according to presentation[18]:

(1) Sudden onset of dyspnoea, possibly with pleuritic pain and/or haemoptysis but haemodynamically stable (most common), (2) sudden onset of haemodynamic instability, possibly with syncope and usually with RV strain, and (3) delayed onset (weeks) of dyspnoea and RV strain, mimicking heart failure or indolent pneumonia (least common).

Signs and symptoms

Although most patients with diagnosed PE experience symptoms, these symptoms are common in many other diseases and conditions.

In two studies[11, 19] of 2454 and 800 patients respectively with PE, the most common signs and symptoms were identical in terms of order: dyspnoea (78-81% and 82%), chest pain (39-56% and 49%), syncope (22-26% and 14%), and haemoptysis (5-7% and 7%). In the study of 800 patients, 756 (94%) had at least one of the four symptoms listed above, and only 7 (1%) had no symptoms before diagnosis.

In another study of 117 patients with PE, 113 (97%) had either dyspnoea, tachypnea, or pleuritic pain[20].

Electrocardiogram

An electrocardiogram (ECG) of a patient with suspected PE is important mostly for excluding other diagnosis, such as myocardial infarction, as PE usually causes non-specific changes. However, sinus tachycardia is common, and in PE with an effect on haemodynamics, right heart strain (e.g. T wave inversion) may be seen. These findings can strengthen the likelihood of PE when combined with a clinical assessment of symptoms and risk factors. The classic S1Q3T3 pattern (S wave in lead 1, Q wave and inverted T wave in lead III) is often thought of as pathognomonic of PE, it is however rather rare, and some studies even suggest it is as likely to be found in patients without PE[18, 21].

Wells score

Given the relatively low sensitivity and specificity of individual signs, symptoms and findings for PE, a standardized prediction rule for assessing the pre-test probability of PE is often recommended. The most common of these rules is the Wells rule, which consists of seven factors:

Table 2 – Components of the Wells rule and their scores.

Wells rule	Score
Haemoptysis	1
Active cancer	1
Previous PE/DVT	1.5
Heart rate ≥100 BPM	1.5
Surgery or immobilization within 4 weeks	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3

The clinical probability is then divided into low (0-1 points), intermediate (2-6 points) and high (≥7), which translates into approximate percentages of patients who can be expected to have confirmed PE of 10%, 30%, and 65% respectively. The probability can then help guide the physician in his or her overall assessment and course of action for the patient[7].

Diagnosing Pulmonary Embolism

Due to the often non-specific signs and symptoms of PE, it is difficult to suspect in the "right" patient. This is reflected in everyday clinical work where initial testing for suspected PE is nondiagnostic in approximately 30-70% of patients. Complicating the matter further, the prevalence of PE in these patients with nondiagnostic testing is about 20%[20, 22]. As a result of this difficulty to suspect and diagnose PE in patients who suffer from it, the condition is still underdiagnosed to a great extent. A survey examining almost 60 years (1945-2002) of relevant literature found that 3268/3876 (84%) of patients with PE at autopsy were not diagnosed or suspected of having it while still alive, and this was also true for the

2448 patients who were deemed to have large or fatal PE, where 1902 (78%) were neither diagnosed nor suspected[19].

D-dimer

D-dimer is a fibrin breakdown product which can be found at elevated levels in plasma when coagulation and fibrinolysis are activated simultaneously. This process occurs during acute thrombosis, why D-dimer has a high negative predictive value (NPV) in venous thromboembolism (VTE), however, there are numerous other causes of fibrin production and its consequent degradation, such as trauma, surgery, bleeding, inflammation, and cancer. As such D-dimer has a low positive predictive value (PPV), meaning that it is not useful for the confirmation of PE, but instead can be used to rule-out PE in patients with low probability (0-1 Wells score)[7]. A study of 437 patients with a low probability of PE showed a NPV of 99.5% using a D-dimer test[23]. In Sweden, the National Board of Health and Welfare's guidelines state that a D-dimer test should be taken for patients with 0-2 Wells score, and if positive (or if the patient has a Wells score of ≥3) the next step should be a CT of the pulmonary arteries[24].

Echocardiography

Although echocardiography rarely shows direct signs of PE (emboli in the central pulmonary arteries or mobile thrombi in the heart), indirect signs such as a disturbed RV ejection pattern (60-60 sign), or depressed contractility of the RV free wall compared with the apex (McConell sign), have a high PPV and can lead to a PE diagnosis[25]. While at least 25% of PE patients have RV dilation it is not specific to PE, nonetheless it is useful for risk stratification of patients, as RV dilation is associated with higher mortality in PE. The overall NPV of echocardiography is roughly 40-50% and therefore cannot be used to exclude PE. In patients with suspected high-risk PE, absence of RV dilation or dysfunction more or less excludes PE as the cause of haemodynamic instability. In these patients, an echocardiography

is useful in identifying and/or excluding other causes of circulatory shock, such as cardiac tamponade, aortic dissection, left ventricle dysfunction, and hypovolaemia[7, 18].

Computed tomography

Although conventional pulmonary angiography has higher sensitivity and specificity for diagnosing PE, CT angiography has widely become the method of choice for doing so, since the introduction of multi-detector computed tomographic (MDCT) angiography. This can be attributed to its speed, ability to visualize the pulmonary arteries and the heart with potential dilation of the RV, high interobserver agreement, and the possibility to diagnose other conditions of the lung and heart that may be causing the patient's symptoms[7, 18]. The diagnostic criteria of PE on a CT scan include: partial or complete filling defect of contrast in the lumen (which can be seen as areas of low attenuation with surrounding contrast medium), masses floating in the lumen (railway track sign), a peripheral intraluminal filling defect that forms an acute angle with the artery wall, and contrast material between a central filling defect and the artery wall[18, 26].

A prospective multicentre trial investigating the accuracy of MDCT angiography in 824 patients concluded that the overall sensitivity was 83% and specificity 96%. The results showed that MDCT is most useful for ruling out PE in patients with a low or intermediate clinical probability (categorized by the Wells rule), with a NPV of 96% and 89% respectively, as well as confirming PE in patients with an intermediate or high clinical probability (PPV of 92% and 96% respectively). When it came to ruling out PE in patients with a high clinical probability, or confirming PE in patients with a low clinical probability, the MDCT was much less accurate, with a NPV of only 60% in the former, and a PPV of 58% in the latter. This highlights the importance of not disregarding the clinical assessment of a patient, particularly when there is discordance between this assessment and the results of a test such as a CT scan[26].

Pulmonary angiography

Pulmonary angiography is the gold standard for diagnosing PE when it comes to specificity and sensitivity, but is less frequently used since the improvement of CT imaging has led to similar accuracy. Other reasons include that it is more time consuming, more operator dependent, less available, and most importantly, due to its invasive nature, it carries a procedure-related mortality of approximately 0.5%, and a non-fatal major complication rate of 5%. Nevertheless it is still useful in some cases, e.g. when other diagnostic methods are inconclusive[18, 27].

Pathophysiology

Acute PE and deep-vein thrombosis (DVT) are two conditions stemming from the same process of VTE and are thus intricately linked. There is evidence suggesting that DVT precedes PE in approximately 70% of cases, and in a majority of the remaining cases the absence of DVT is thought to be attributed to the complete detachment of the thrombus from deep veins. Conversely, some form of PE can be found in roughly 40-50% of patients presenting with proximal DVT (v. poplitea or more proximal), although these are often asymptomatic[17, 28].

Thrombosis in veins occur when there is an unfavourable imbalance in the coagulation haemostasis, which can be summarized in the so-called Virchow´s triad, consisting of factors that affects the bloods tendency to clot. These can be divided into three categories: (1) haemodynamical (stasis or turbulence of blood), (2) vessel wall impairment (endothelial injury or dysfunction), and (3) hypercoagulability of blood (high levels of coagulative factors, and/or defects in anti-coagulative factors)

Impaired blood flow can create a hypercoagulable micro-environment in proximity to venous valves, where thrombosis is thought to begin, and can occur during long periods of

immobility, such as prolonged bed-rest or having lower-limb paralysis. Obstruction of blood flow can also be caused by external objects pressing on the vein, such as enlarged lymph nodes, or a tumour. Damage to the vessel leads to exposure of procoagulant membrane surfaces, and is usually caused by surgery, but can also arise from trauma. An imbalance in coagulative and anti-coagulative factors can have several causes, such as natural ageing, increased estrogen levels in women (e.g. from oral contraceptives or hormone replacement therapy), certain diseases (e.g. polycythemia vera), inherited factors (e.g. protein-C deficiency), and cancer [29, 30].

Risk Factors

The risk factors for VTE can be divided into two major categories: patient characteristics and triggering events. Patient characteristics include body composition, age, previous VTE, and genetic factors. Triggering events include recent surgery, immobilization/hospitalization, presence of cancer, exogenous contraceptives/hormone replacements, travel, infection, trauma, and pregnancy. Half of all thrombotic events are thought to be caused by such events, and in about two thirds of these cases the presence of more than one factor can be identified. In a study of almost 22 000 patients, over an eight-year period, the most common risk factors for VTE were hospitalization (52%), cancer (48%), and recent surgery (37%)[31, 32].

Hospitalization and surgery

Due to the associated conditions of being hospitalized, such as immobilization, infection, cancer, and surgery, up to 20% of patients admitted will suffer from VTE, and up to 40% of those who have surgery. Although all of these are not clinically relevant at the time of diagnosis, they increase the short-term risk of symptomatic PE and other VTE-related complications[31]. In the International Cooperative Pulmonary Embolism Registry (ICOPER), a large multicentre study of 2110 patients with PE, 29% had undergone surgery in the last

two months, although 50% of these patients had not received perioperative VTE-prophylaxis[11].

Cancer

Cancer increases the risk of venous thrombosis by roughly 6-10 times, and does so in a multifaceted way, through changes in both patient characteristics and triggering events. Cancer patients are often subjected to hospitalization, surgery, and chaemotherapy, all of which are independent risk factors of VTE. As mentioned previously, some cancers apply direct pressure onto veins, compromising their ability to keep the blood circulating. Furthermore, cancer cells interfere with normal coagulative pathways by shedding procoagulative particles, such as tissue factor and membrane lipids[29, 31].

Obesity

Obesity, defined as a body-mass index (BMI) of more than 30 kg/m^2, is associated with an increased risk of VTE by two to three times. The risk is higher still for individuals with an even greater BMI (>40). Although the exact mechanism behind the increased risk of VTE in obesity is not known, impaired venous return, increased coagulation, and inflammation, are all thought to play a role[31].

Right ventricle dilation in pulmonary embolism

Right ventricle dysfunction (RVD) is defined according to the European Society of Cardiology on computed tomographic (CT) angiography as a RV/LV diameter ratio of ≥0.9 or ≥1.0. Echocardiographic criteria are RV/LV diameter ratio of ≥0.9 or ≥1.0, and/or an increased end-diastolic RV–LV diameter ratio; hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above[7]. RVD is associated with an increased risk of death in patients with PE, regardless of whether haemodynamic instability is present or not. However, even if 95% of the patients who die from PE have signs of RVD, it is predictive of death in only 10% of all patients with RVD. This is the reason

why RVD is not an independent indication for thrombolysis or other forms of aggressive treatment. Examination for RVD could however be useful when deciding which patients can be treated at home.

One study published in 2005 of 120 patients with PE and haemodynamical stability showed a significantly higher mean RV/LV ratio at CT in patients that died due to PE (1.54 ± 0.18), than patients who survived (1.14 ± 0.03, p = 0.005), and patients who died of causes unrelated to PE (1.17 ± 0.08, p = 0.033). Of the seven patients who died from PE, four had a ratio between 1 and 1.5, and three had a ratio over 1.5[33]. In contrast, a study published two years earlier of 173 patients with PE of low to moderate severity, and a mean RV/LV ratio of 1.1, showed no correlation between RV/LV ratio and death[34]. A later study suggested that this lack of correlation may have been due the use of five different types of CT scanners, as well as the fact that a PE protocol was not used in the scanning of some patients[35].

In a study of more critically ill patients published in 2006 the authors concluded that RV/LV ratio and azygos vein diameter, at CT pulmonary angiography, were the best predictors of survival amongst cardiovascular parameters. The study included 82 patients with PE who were treated in an intensive care unit and had CT available for review. Mean RV/LV ratio in survivors (n=70) was 1.3 ± 0.4 vs. 1.8 ± 0.6 (p=0.011) in non-survivors (n=12). When analysing threshold values of RV/LV ratio as predictive of death, a higher value indicated a higher probability of death for all measurements. A ratio of ≤1 gave a probability of 5%, and a ratio of 2.3 a probability of 50%. A threshold value for RV/LV ratio of 1.5 yielded optimal sensitivity 69% and specificity 69% in discriminating survivors from non-survivors[36]. A more recent study from 2010 of 48 patients, showed similar results and concluded that a RV/LV ratio >1.5 was a useful diagnostic criterion for severe PE and poor patient outcome. The patients were divided into three groups based on their RV/LV ratio, <1 (n=18), 1-1.5 (n=15) and >1.5 (n=15). At 30 days the mortality rate was 40% for patients with a ratio of

>1.5, 20% for 1-1.5, and 0% for <1. The mean RV/LV ratio in survivors was 1.2 ± 0.5 vs. non-survivors 1.6 ± 0.5 ($p<0.05$)[35].

A meta-analysis from 2014 of 27 studies and 4767 patients with PE found an association between RVD at CT, and death at 30 days and 3 months (Table 2). The association was confirmed in analyses of death due to PE, and was also found in subgroup analyses of normotensive patients. Trials with a higher cut-off point for RVD (≥1) had a higher odds-ratio (2.81 vs. 1.99) than trials with a lower cut-off point (≥0.9)[37].

Table 3 - Odds-ratios for all-cause death in the presence of right ventricle dilation in a meta-analysis of PE (Beccatini et al., 2014).

	n	Odds-ratio	95% CI	p-value	I^2 %
Overall	4767	2.11	1.61-2.76	<0.00001	44
30 days (RVD cut-off 0.9)	2304	1.99	1.38-2.86	0.0002	22
30 days (RVD cut-off 1/1.01)	1678	2.81	1.78-4.42	<0.00001	0
3 months	782	4.65	1.79-12.07	0.002	51
Death due to PE	2925	7.35	3.59-15.09	<0.00001	16
Normotensive patients	2254	1.64	1.06-2.52	0.03	0

A meta-analysis published a year later (2015) of 49 studies and 13 162 patients showed similar results, with an approximate 2.5-fold risk for all-cause mortality, and a 5-fold risk for PE-related mortality, being associated with an RV/LV ratio ≥1.0 on CT. RV/LV ratio was concluded to have the strongest predictive value for adverse clinical outcomes of all CT parameters[38].

Treatment of Pulmonary Embolism

The purpose of treatment in pulmonary embolism is twofold: to decrease the harmful and potentially fatal physiological strain in the acute phase, and to decrease the risk of recurrent VTE in both the short- and long term.

The choice between anticoagulation or advanced treatment, such as thrombolysis or surgery, is usually determined by the presence of haemodynamic instability and/or heart strain, as well as the patients' eligibility of receiving these advanced treatments. Although most cases should be primarily treated with systemic anticoagulation (heparin or heparin-derivatives) and/or with systemic thrombolysis, CDI has become an increasingly utilized treatment for patients with contraindication to, or little effect from, these first-line treatments. While meta-analyses of CDI have reported high rates of clinical success, combined with a low risk of serious adverse events (such as major bleeding otherwise common in treatments with systemic thrombolysis), most studies conducted are retrospective, and very few are controlled or randomized[39, 40].

Anticoagulation

Anticoagulation is the first line of treatment in patients with low- and intermediate-risk PE, and should be given as prophylaxis for at least three months (and longer or lifelong depending on circumstances) after the PE-event, regardless of severity. In the acute-phase administration of parenteral anticoagulation is recommended, such as unfractionated heparin, low molecular weight heparin, or fondaparinux, over the first 5-10 days. This treatment should be overlapped (preferably as soon as possible) with the start of oral anticoagulants such as a vitamin K antagonist (VKA, e.g. warfarin) which has been the gold standard for decades; in recent years however, direct oral anticoagulants have replaced VKAs at an increasing rate, as they have been shown to be as effective in preventing recurrent VTE, but with a smaller risk of bleeding, and without the need to monitor the therapeutic range of international normalized ratio (INR) as for VKAs[7].

Advanced treatment

Advanced treatments in PE aim to quickly restore pulmonary reperfusion, decrease pressure and resistance in the pulmonary arteries, and consequently RV overload and strain, with the

ultimate goal of reversing haemodynamic decompensation. These treatment options consist of thrombolysis, surgical embolectomy, CDI and extracorporeal membrane oxygenation (ECMO). Due to their risk/benefit profiles and demand of resources they are generally reserved for patients with high-risk PE, with the exception of CDI which is frequently used as treatment of intermediate-risk PE[7, 41].

Surgical embolectomy of PE is especially effective in patients who have mobile heart thrombi, a patent foramen ovale (which can lead to stroke), or who have had insufficient effect from thrombolysis[41]. Although the procedure is rare compared to the other advanced treatments, the reported 30-day survival rate in high-risk PE is as high as 94% in some centres[42].

ECMO is a technique of cardiopulmonary support that oxygenates blood drained from the venous system outside of the body, and then returns it to the arterial system, eliminating the need for a patient to oxygenate the blood through the pulmonary circulation. In PE it can stabilize patients with haemodynamic instability and buy time to determine which treatment strategy is optimal to go forward with. It can also be used in conjunction with thrombolysis, CDI, or as a bridge to surgical embolectomy[43]. Thrombolysis and CDI will be discussed later on in this paper.

Catheter-Directed Interventions

Modern CDI consists primarily of five different techniques: (1) thrombus fragmentation (e.g. with a hooked or rotating pigtail catheter) which is a type of mechanical fragmentation with the goal of breaking up the thrombus into smaller emboli that pass to the microcirculation, (2) suction thrombectomy through aspiration of the thrombus through large-lumen catheters using negative pressure generated with an aspiration syringe, (3) combined fragmentation and suctioning through a catheter that at the tip combines a rotational coil with aspiration ports.

The rotation of the coil creates a negative pressure which makes the thrombus pervious to aspiration, (4) rheolytic thrombectomy (AngioJet®) which uses high-pressure saline jets that fragment the thrombus and produces a vacuum that allows for aspiration, and (5) catheter-directed thrombolysis (CDT) using a local infusion of a thrombolytic drug, e.g. tPA 0.5-2.0 mg per hour and catheter for up to 24 hours.

The first four techniques are mechanical, and can be used by themselves or be combined, and are suitable even for patients with absolute contraindications for thrombolysis. Patients with a relative contraindication (or no contraindication) for thrombolysis can be treated with mechanical interventions alone, or in addition to CDT (so called pharmacomechanical thrombolysis)[44]. Moreover, it seems that the effect of CDT can be enhanced with the addition of high-frequency low power ultrasound, which makes the thrombus more permeable to the thrombolytic drug, but further research is required to establish this effect[40].

Side effects of rheolytic thrombectomy

There has been some concern over the use of AngioJet® due to its potentially harmful side effects, most notably bradychardia with risk of cardiac arrest. The mechanism is possibly the release of arrhythmogenic and vasoactive substances, such as potassium, bradykinin, and adenosine. Haemolysis, impairing renal function and causing haematuria, is another common side-effect, but is usually reversible without any long-term effects[44].

While some small independent studies support the safety of AngioJet® [45, 46], a meta-analysis of CDI from 2009 showed adverse results; the highest complication rates were found in the 68/594 patients (11%) who were treated with AngioJet®, with 27 minor complications (40% vs. 7.9% in all patients), and 19 major complications (28% vs. 2.4%), including five major haemmoraghes and five procedure-related deaths[39]. AngioJet® was used in 68/594 (11%) of the studied patients, but 19/25 (76%) of all major complications were attributed to it, and it was the only device associated with procedure-related deaths[39]. Due to these procedure-

related complications, some advice against using the AngioJet® at all, and the American Food and Drug Administration (FDA) has issued a so called “black box warning” on the AngioJet®, which is their strictest warning regarding hazard in association with a treatment[1, 47].

Effectiveness of different treatment strategies

Systemic thrombolysis is the first line of treatment for high-risk PE, but its use in intermediate-risk PE has been controversial due to a less favourable benefit-risk ratio. A meta-analysis of 11 randomized trials (1973-2002) and 748 patients who had either intermediate-risk or high-risk PE and were treated with either heparin or heparin + thrombolysis, indicated a mortality rate (up to 30 days or in-hospital) of 6.2% for thrombolysis vs. 12.7% for heparin (OR 0.47 95% CI: 0.20-1.10). However, thrombolysis was associated with an increased frequency of major bleeding (21.9% vs. 11.9%, OR 1.98 95% CI: 1.00-3.92)[48].

In a retrospective study of 72 230 patients with PE comparing thrombolysis to no thrombolysis in patients who were unstable (defined as either in shock or ventilator dependent) and treated in the U.S between 1999 and 2008, the 21 390 (30%) patients that had been treated with thrombolysis had an in-hospital all-cause mortality rate of 15%, compared to 47% in the 50 840 (70%) who were not treated with thrombolysis[49].

In a meta-analysis of 8 randomized trials and 1775 patients with intermediate-risk PE, those treated with thrombolysis had a mortality rate of 1.39% (OR, 0.48; 95% CI: 0.25-0.92) vs. 2.92% in those treated with anticoagulant. Major bleeding rate was 7.74% vs. 2.25% (OR, 3.19; 95% CI: 2.07-4.92)[50].

In a systematic review and meta-analysis from 2009 (Kuo et al.) of high-risk PE, 594 patients from 35 different studies (1991-2008) who were treated with CDI were analysed regarding clinical success, defined as stabilization of haemodynamics, resolution of hypoxia, and

survival from high-risk PE. 33% of patients in the analysis were treated with mechanical intervention alone, whereas 60%-67% were treated with pharmacomechanical thrombolysis. Pigtail fragmentation was the most commonly used technique, being the only mechanical technique in 53% of cases, and in 69% of the total study group. After heparin, the next treatment in line was CDI, applied in proportion of 95% of the patients. Pooled clinical success rate was 86.5% (95% CI: 82.1%-90.2%, I2 = 40,3%). Major complications (e.g. major haemorraghe) related to the procedure were rare (2.4% (95% CI: 1.9%-4.3%), especially when put in contrast to the estimated risk of up to 20% of major haemorraghe from systemic thrombolysis. However, one should keep in mind that all studies included in the review were non-controlled, that there was considerable variation in CDI-techniques (e.g. with/without CDT), and that the range of clinical success rate between studies was large (40%-100%)[39].

A more recent meta-analysis (2018) examined CDT in 20 studies (2009-2017) and 1168 patients. The 30-day mortality estimate was 8.0% (95% CI: 3.2%-14.0%, I^2 = 49.4%) in patients with high-risk PE (n: 210), and 0% (95% CI: 0%-0.5%, I^2 = 10.9%) for intermediate-riskPE (n: 945), major bleeding was estimated at 6.7% (95% CI: 1.0%-15.3%) and 1.4% (95% CI: 0.3%-2.8%) respectively. 11/20 studies reported on RV/LV ratio, with a pooled mean of 1.3, and a mean decrease of 0.30 (95% CI: 0.22%-0.39%) after intervention. Notable for this study was the relatively low age of the included patients (mean 59 years, range 53-65 years), which may have contributed to the low mortality rate[40].

As of yet, there are no randomized trials that have compared CDI to any other treatment in patients with high-risk PE[51]. In a randomized trial of 59 patients with intermediate-risk PE who received either ultrasound-assisted catheter-directed thrombolysis (USAT) + unfractionated heparin, or unfractionated heparin alone, results were in favour of the USAT-group, with a mean decrease in RV/LV ratio from baseline to 24 hours of 0.30±0.20 versus

0.03±0.16 (*P*<0.001), and no statistically significant difference in bleeding complications[17]. In a prospective single-arm multicentre study published in 2019 of 104 patients with intermediate-risk PE, and a baseline RV/LV ratio of 1.56, who were treated with mechanical thrombectomy (the FlowTriever System) in addition to anticoagulation, the average decrease in RV/LV ratio at 48 hours was 0.38 (p <0.0001). One patient (1%) died within 30 days, due to undiagnosed breast cancer. This was the largest study to date evaluating the effectiveness of mechanical thrombectomy in PE[52].

Research question

In 2013 a new treatment algorithm for PE was introduced at Sahlgrenska University Hospital. This algorithm included CDI for patients with high-risk PE and contraindication to systemic thrombolysis.

The aim of this study was to evaluate the results of the newly introduced CDI method used for treating patients with high-risk PE and contraindication to systemic thrombolysis.

We hypothesized that there is no difference as to mortality rate and RVD reversal between CDI and anticoagulation when used for treating patients with high-risk PE and contraindication to systemic thrombolysis.

Methods

Design

We used prospectively registered data from medical records and quality registries to conduct a retrospective analysis of outcomes from CDI treatment between July 2013 and December 2018 in patients with high-risk PE. For historical controls, we used a cohort of patients with high-risk PE who had been treated with anticoagulants only between January 2006 and June 2013 (Figure 1).

Inclusion

Eligible patients were identified either in the local database of the central intensive care unit by the diagnosis code for PE or the treatment code for thrombolysis between 2006 and 2016 or in the radiology database by the treatment code for CDI during 2013-2018.

Inclusion criteria: (1) pulmonary embolism, diagnosed either at CT or by clinical assessment, (2) haemodynamic instability, defined as either SBT <90, or syncope, at any time, (3) RV/LV ratio ≥0,9 at CT or echocardiography, (4) contraindication(s) for thrombolysis, determined by clinical assessment, and (5) age ≥ 18 years.

Exclusion criteria (control group): (1) PE treated with CDI or surgery and (2) no treatment for PE.

Exclusion criterion (experimental group): (1) no active treatment during CDI.

RV/LV ratio

All measurements of RV/LV ratios available from CT were performed by one single radiology specialist. All RV/LV ratios available from echocardiography were measured by an anesthesiology specialist certified in echocardiography. These specialists were blinded to the results of each other's measurements and to patient outcomes.

If a patient had had both CT and echocardiography, the measurements on CT were used in the analyses, as they were deemed to be of higher relevance to this study.

Outcomes

Primary outcome was survival at 90 days from the PE event.

Secondary outcomes were: RV/LV ratio, number of days in hospital, number of hours in the ICU, s-Creatinine, TnT, NT-proBNP. The most abnormal value within 24 hours before/after treatment was used.

Statistical Methods

Descriptive statistics were used for group characteristics and outcomes. Reported means were specified to the one- decimal level (standard deviation) for secondary outcomes, and two-decimal level for RV/LV ratio. The Shapiro-Wilks test was used to confirm normal distribution. Comparison between groups of the primary outcome survival at 90 days was performed using the chi-square test and comparison of secondary outcomes was performed using the independent-samples t test (parametric assumptions satisfied), or Mann-Whitney U-test (parametric assumptions not satisfied). A linear mixed model, with adjustment for timing of pre- and post-treatment imaging, was used to compare the rate of decrease of RV/LV ratio between groups.

Ethical considerations

Seeking the patients', or in case of death their relatives', approval for conducting this study was deemed a larger burden for them than the relatively small breach of integrity of reviewing their medical records for the purposes of this study. Nevertheless, the recording of data from classified medical records without the patients′ knowledge or approval requires protection of personal integrity by the researchers. All personal information was registered and stored on secured servers, accessible only by the investigators. Any result from analysis is presented on the group level without any information that might reveal individual identities. Under these conditions, the study was approved by the Regional Research Ethics Committee of Gothenburg in February 2019 (No. 00827).

Results

In total, 45 patients were included in the study (Figure 1). There were 23 patients who met all criteria for the control group, of which 18 had PE diagnosed by CT whereas five had been indirectly diagnosed by clinical assessment and echocardiography.

There were 22 patients who met all criteria for the CDI group. Three patients were not haemodynamically unstable at presentation, but had significant RV dilation (RV/LV ratio 1.8, 2.7 and 3.1, respectively) and strain and were therefore included in the analysis. 20/22 (91%) in the CDI group were treated with the AngioJet® rheolytic system.

Three patients in the control group, and two patients in the CDI group, were treated with systemic thrombolysis despite identified contraindications.

The groups were similar regarding age and gender distribution (Table 3), and the CDI group had a trend toward higher PESI-scores (Table 4).

Table 4 – Group characteristics

	CDI (n=22)	Control (n=23)
Age (mean)	67.1	68.2
Age (range)	38-81	52-83
Female	50%	61%
Systemic thrombolysis	2	3

Table 5 – PESI-scores

	PESI-score		P-value
CDI vs Control (mean)	188	168	0.124
CDI vs Control (range)	119-289	92-233	
Survivors vs non-survivors (mean)	169	190	0.104

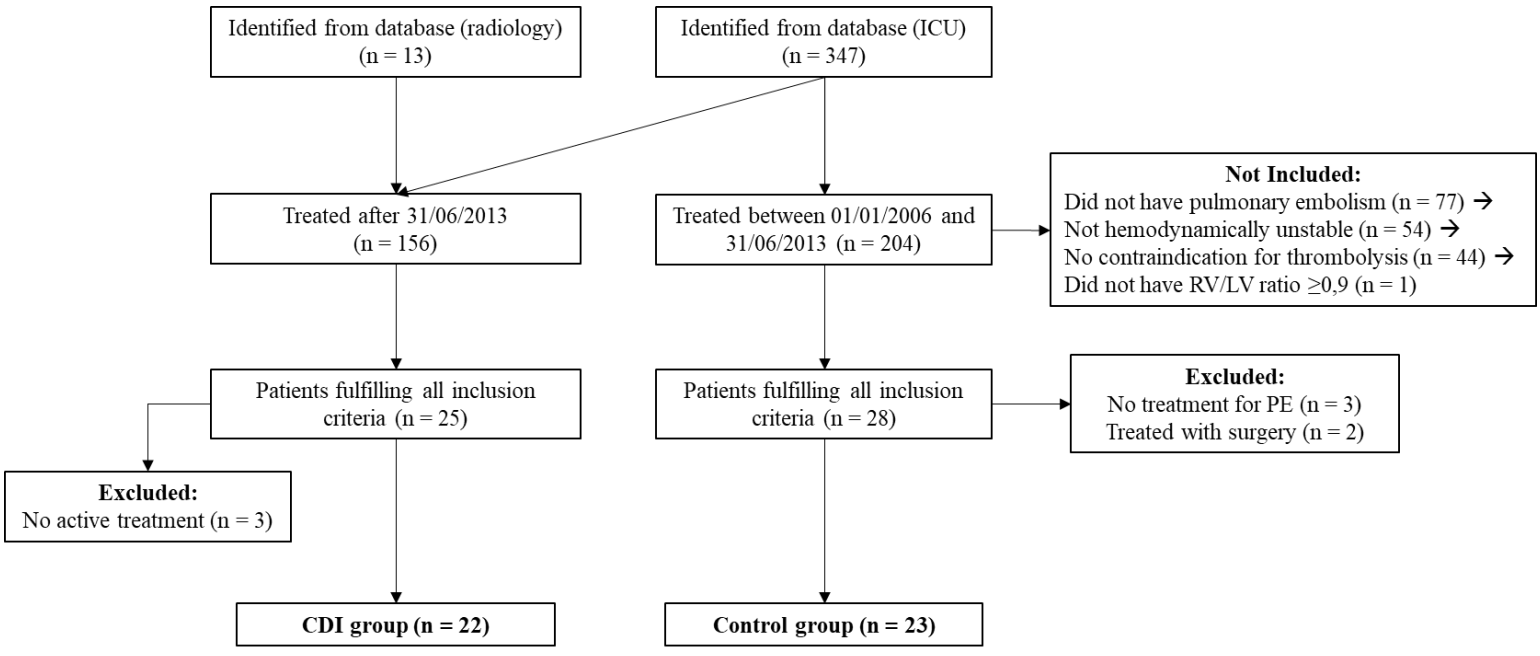

Figure 1 – Flow chart of inclusion and exclusion of participants in the trial group

Primary outcome

The 90-day mortality (Figure 2) did not differ between the groups, 13/22 (59%) in the CDI group and 14/23 (61%) in the control group were still alive at 90 days (p=0.903). In a Kaplan-Meier graph (Figure 3) describing survival over three years, the survival rate was similar between the groups for all timepoints.

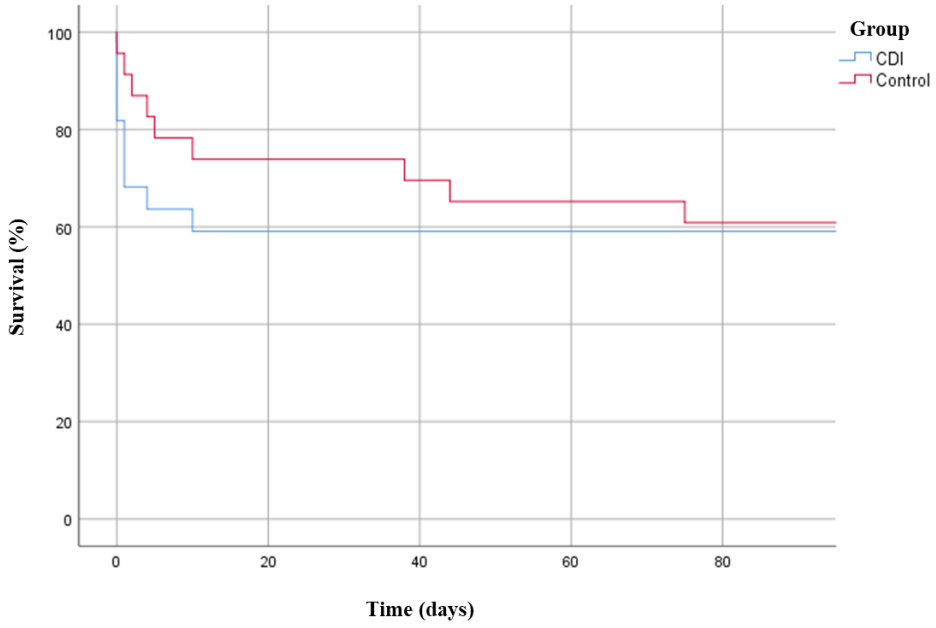

Figure 2 – Kaplan-Meier survival graph for the first 90 days.

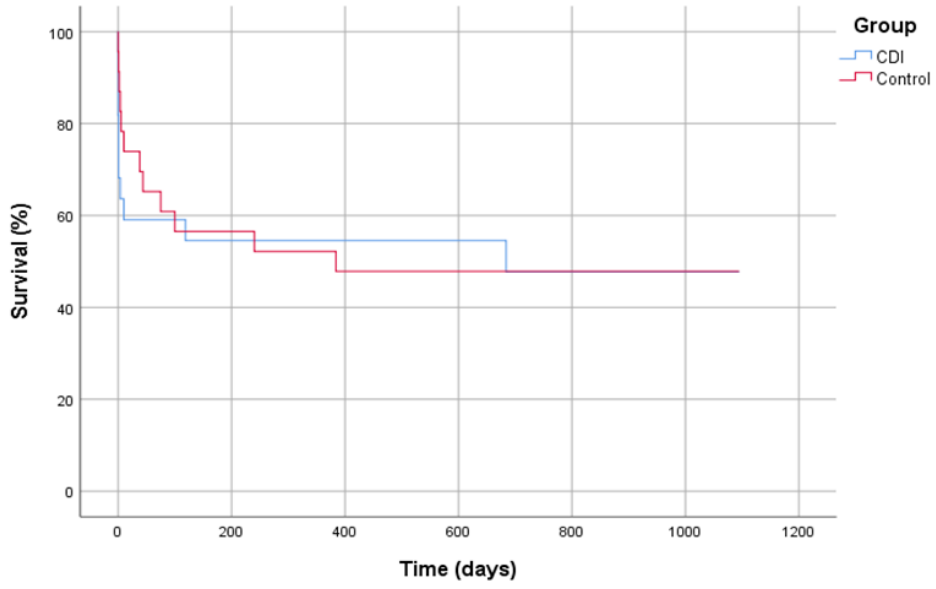

Figure 3 – Kaplan-Meier survival graph for the first three years.

Secondary outcomes

The CDI group had shorter hospital stays as well as shorter ICU stays (Table 6), however only the former was statistically significant. When removing the patients who died during admission of either the hospital or the ICU, the relationship remained in the analysis of days in hospital, but there was no difference in hours in the ICU between the groups.

Table 6 – Days in hospital and hours in the ICU

	CDI (n=22)	Control (n=23)	p-value
Days in hospital, mean (SD)	10,2 (11)	26,0 (27)	0,01
Days in hospital (survived to discharge) mean (SD)	16,0 (10)	29,2 (22)	0,05
Hours in the ICU	69,5 (91)	97,7 (191)	0,53
Hours in the ICU (survived to discharge) mean (SD)	86,3 (98)	98,5 (201)	0,84

In the analyses of laboratory markers (Table 7), the CDI group had on average an increase in s-Creatinine after treatment, while the control group had a slight decrease. In the CDI group 16 had s-Creatinine measured both pre- and post-treatment, compared to 17 in the control group, for TnT CDI 5 vs. 2 control, and only two patients (both CDI) had NT-proBNP before and after treatment, why no analysis was done.

Table 7 – Analyses of changes in laboratory markers pre- and post-treatment.

	CDI (n=16)	Control (n=17)	p-value
Δs-Creatinine (µmol/L) mean (SD)	24,9 (21,7)	-6,7 (51,3)	0,01
	CDI (n=5)	**Control (n=2)**	
ΔTnT (ng/L) mean (SD)	-119 (166)	74 (144)	0,21
ΔNT-proBNP	-	-	-

RV/LV ratio

The RV/LV ratio before treatment available from CT in 38 patients (22 CDI, 16 control), differed between the groups; CDI 2.15 (0.69) (range 1.2-3.5) vs. 1.42 (0.40) control (range 0.8-2.2) p<0,001.

Another four patients in the control group had an RV/LV ratio measurable from echocardiography before treatment, when including them in the analysis (22 CDI 20 control) the difference remained between the groups; CDI 2.15 (0.69) vs. 1.40 (0.36) control (p<0,0001).

19/22 (86%) in the CDI group had an RV/LV ratio of ≥1.5 before treatment compared with 6/20 (30%) in the control group.

RV/LV ratio was not a predictor of death, mean ratio in survivors was 1.79 (0.69) vs. 1.74 (0.66) non-survivors (F=0.057, p=0.813).

Six patients had imaging at CT before/after treatment, and 23 at CT before and echocardiography after, one patient had at echocardiography before and at CT after.

Mean RV/LV ratio after treatment CDI 1.41 (0.47) vs. 1.08 (0.30) control (p=0.037). ΔRV/LV ratio CDI (n=17) -0.66 (0.84) vs. -0.22 (0.48) control (n=13) p=0.099.

In a linear mixed model (Figure 4) the decrease of RV/LV ratio was 0.4 units higher per 24 hours in the CDI group than the control group (p=0.007).

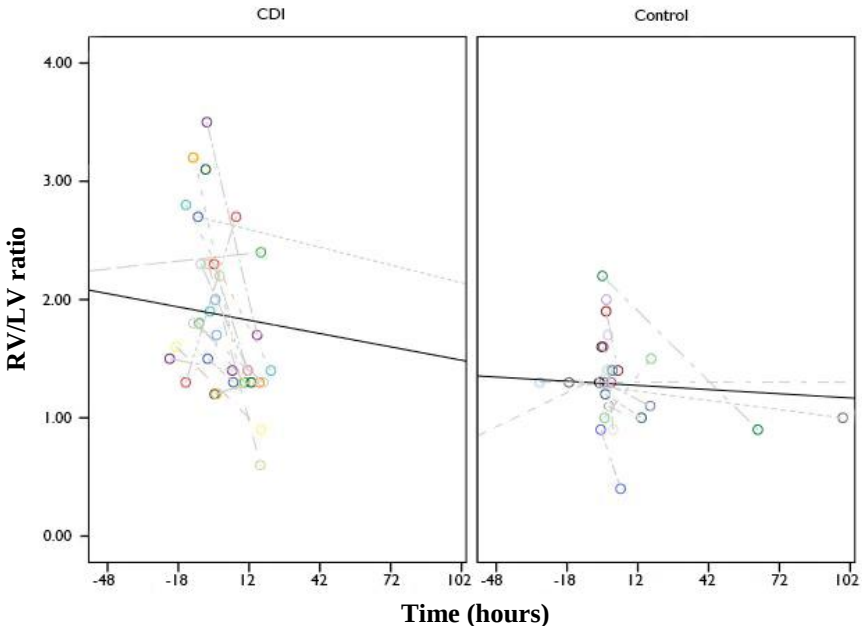

Figure 4 - Graph of linear mixed model of ΔRV/LV ratio pre- and post-treatment when adjusted for time. The black line represents the group's average change.

Discussion

In patients with high-risk PE and contraindication to systemic thrombolysis, there was no difference in survival at 90-days between two cohorts who had been treated with anticoagulation or CDI respectively. Both groups were well matched with regard to gender and age, however, the CDI group was under greater physiological strain as their mean RV/LV ratio was significantly higher than the control group, and they had a trend toward higher PESI-scores.

Although higher RV/LV ratios were not a predictor of death in our material previous studies have established this correlation[35-38]. The reason that this association was absent in this study was possibly due to the overall rather small sample size. Even though the CDI group had much higher RV/LV ratios at baseline the survival rate did not differ significantly between the groups for any point in time (survival from ICU, survival from hospital, 30-days, and 90-days), which could be interpreted as such that CDI in fact is more effective than anticoagulation for this patient population. Thus, for this specific and poorly studied patient population of patients with both high-risk PE and contraindication to thrombolysis, randomized trials comparing CDI to anticoagulation would yield more robust data as to which of the treatments is preferable.

When comparing the rate of decrease in RV/LV ratio between treatments, CDI was more effective, with a decrease of 0.4 units higher per 24 hours. This is in line with the only randomized trial comparing CDI to anticoagulation alone in PE[17], as well as the recently published FLARE study, which was the largest individual study to date of mechanical thrombectomy in PE[52]. However, both of these trials were conducted in patients with intermediate-risk PE, and in the former, the technique used was CDT, which is fundamentally different to the AngioJet® system mainly used in our patients.

Early haemodynamic improvement has been shown to be associated with better long-term outcomes in PE, although this association is not yet well established. In one trial 72 patients with intermediate-risk PE were randomized to either 100 mg alteplase + heparin or placebo + heparin, with favourable results for alteplase in improvement of RV function, which persisted at the end of the follow up at 6 months[53]. Another trial of 23 patients randomized to either heparin or thrombolysis, showed favourable results for the thrombolysis group in regard to mean pulmonary artery pressure, pulmonary vascular resistance, and haemodynamic response to exercise, after a mean follow-up of 7.4 years[54].

A potential advantage of CDI over anticoagulation is reduced resource expenditure, due to shorter ICU and hospital stays. The reason for this may be that CDI results in faster cardiovascular relief, preventing further deterioration and more quickly reversing the pathological physiology caused by the PE, both of which could reduce the patients' need of care. In our material, the CDI group had significantly shorter stays in the hospital, but not in the ICU. The recently published FLARE study of 106 patients treated with mechanical CDI concluded that a potential advantage of CDI was reduced need for post-procedural critical care[52].

To our knowledge, there have been no studies designed to compare different CDI-techniques to each other. As such, the technique of choice can differ between hospitals in accordance with preference and tradition. At our hospital the AngioJet® system has been used routinely since 2013, even though the meta-analysis from Kuo et al showed in 2009 that this technique is associated with an increased risk of procedural complications[39]. To minimize the risk for these complications, a protocol has been applied which dictates the maximum application length of the system for each intervention. Since almost all (20/22) of our patients in the CDI group were treated with the AngioJet®, it was shown to be relatively safe in this study, but one cannot rule out more favourable outcomes had a different technique been used. In the last

decade, CDT has become an increasingly popular technique, especially in the US where the AngioJet® system has been issued a black box warning from the FDA[40], and it is possible, if not likely, that this technique will become increasingly utilized in the rest of the world as more studies report favourable outcomes. Furthermore, to fill the current gap in the literature, prospective studies comparing different treatments, and/or different CDI-techniques, in PE are warranted.

Limitations

The limitations of this study were firstly its retrospective design with observational data of differing quality and volume, since no study protocol was applied during the time of treatment. Secondly, the use of an historical control group from a different time period than the experimental group, introducing the possibility of selection bias. Lastly, the rather small sample sizes, especially in the secondary outcomes where many patients had missing values for certain parameters, which brought down the statistical power further.

Another limitation was the need to use different imaging techniques (CT and echocardiography) for the measurement of RV/LV ratios. Preferably only one of these techniques should be used to get the most correct measurements, but this was not possible due to very few patients having both CT or echocardiography both pre- and post-treatment. Instead, to minimize the disruption from mixing techniques, all pre-treatment measurements were calculated from CT, and all post-treatment measurements from echocardiography.

Conclusions and Implications

In this retrospective observational study of CDI in patients with high-risk PE and contraindications to thrombolysis, this treatment was as effective as treatment by anticoagulation (or thrombolysis) with regards to survival. However, CDI resulted in faster resolution of RV dilation, which hypothetically could prevent further haemodynamic decompensation in some patients. However, the latter is to be interpreted with caution since

the patients in the CDI group had higher pre-treatment RV/LV ratios. Prospective and randomized trials are warranted to more accurately evaluate the effectiveness of CDI in high-risk PE.

Kateterbehandling av högrisk lungemboli hos patienter med ökad blödningsrisk

Propp i lungan (lungemboli) är den tredje vanligaste hjärt- och kärlrelaterade dödsorsaken i västvärlden, och uppskattas ligga bakom 5-10% av alla dödsfall som sker inom sluten sjukhusvård. Traditionellt sett så har de flesta patienterna med lungemboli behandlats med blodförtunnande läkemedel, men eftersom vissa anses ha för stor blödningsrisk, eller inte svarar på den mediciniska behandlingen, har man utvecklat och mer frekvent börjat tillämpa andra behandlingssätt vid lungemboli. Dessa alternativa behandlingssätt innefattar framförallt kirurgi och kateterledd behandling.

2013 införde man på Sahlgrenska Universitetssjukhus en behandlingsalgoritm för patienter med en allvarlig typ av lungemboli, där hjärtat och blodcirkulationen är påverkad.
I denna algoritm ingår kateterledd behandling som en del i ledet när patienter anses ha för hög blödningsrisk för blodförtunnande läkemedel, eller när dessa läkemedel inte har tillräcklig effekt.
Sedan man införde denna algoritm på Sahlgrenska har ett 20-tal patienter behandlats med kateterintervention. Det denna studien har undersökt är om det finns någon skillnad i behandlingseffekt hos dessa patienter som fått kateterintervention, jämfört med en kontrollgrupp bestående av liknande patienter som vårdats innan man regelbundet utförde kateterbehandling, och som istället behandlats med blodförtunnande läkemedel.

Det vi såg var att den kateterledda behandlingen var lika bra som läkemedelsbehandling när det kom till överlevnad, då 59% av patienterna som behandlats med kateter hade överlevt

efter 90 dagar, jämfört med 61% hos de som behandlats med läkemedel. Analyser visade att det inte var någon statistisk skillnad på dessa siffror.

Vidare så såg vi att den kateterledda behandlingen var mer effektiv i att snabbt minska belastningen på hjärtat, som skulle kunna hindra ytterligare förfall i vissa patienters hälsa.

Då detta var en så kallad retrospektiv studie, där man studerar patienter i efterhand, så har det en inneboende lägre beviskvalitet än andra typer av studier, där man följer patienter framåt i tiden (s.k. prospektiva studier). Eftersom man såg i den här studien att det var säkert att behandla patienter med kateterledd behandling, kan man nu berättiga att göra prospektiva studier för att bättre undersöka vad det finns för eventuella fördelar och nackdelar med denna typ av behandling, och för vilka patienter den bäst lämpar sig att ta till.

Acknowledgements

The author would like to extend a sincere thank you to Christian Rylander (supervisor) for his role in the formation of this thesis, his general contributions, and as a sounding board. To Jonatan Oras for his help, especially with the collection and processing of data. And to Kristina Svennerholm & Charlotte Sandström for their ideas and contributions.

References

1. Avgerinos ED, Chaer RA. Catheter-directed interventions for acute pulmonary embolism. Journal of Vascular Surgery. 2015;61(2):559-65.
2. Belohlavek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Experimental and clinical cardiology. 2013;18(2):129-38.
3. Piazza G, Goldhaber SZ. Acute pulmonary embolism: part I: epidemiology and diagnosis. Circulation. 2006;114(2):e28-32.
4. Svennerholm K, Lapidus L, Stigendal L, Malm C-J, Zachrisson K, Redfors B, et al. Incidence and Treatment Options for Massive Pulmonary Embolism in Sweden. 2014;15(1_suppl2):15-6.
5. Andersson T, Soderberg S. Incidence of acute pulmonary embolism, related comorbidities and survival; analysis of a Swedish national cohort. BMC cardiovascular disorders. 2017;17(1):155.
6. Sekhri V, Mehta N, Rawat N, Lehrman SG, Aronow WS. Management of massive and nonmassive pulmonary embolism. Archives of medical science : AMS. 2012;8(6):957-69.
7. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)Endorsed by the European Respiratory Society (ERS). European Heart Journal. 2014;35(43):3033-80.
8. Konstantinov IE, Saxena P, Koniuszko MD, Alvarez J, Newman MA. Acute massive pulmonary embolism with cardiopulmonary resuscitation: management and results. Texas Heart Institute journal. 2007;34(1):41-5; discussion 5-6.
9. Janata K, Holzer M, Domanovits H, Mullner M, Bankier A, Kurtaran A, et al. Mortality of patients with pulmonary embolism. Wiener klinische Wochenschrift. 2002;114(17-18):766-72.
10. Bach AG, Taute BM, Baasai N, Wienke A, Meyer HJ, Schramm D, et al. 30-Day Mortality in Acute Pulmonary Embolism: Prognostic Value of Clinical Scores and Anamnestic Features. PloS one. 2016;11(2):e0148728.
11. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet (London, England). 1999;353(9162):1386-9.
12. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic Role of Echocardiography Among Patients With Acute Pulmonary Embolism and a Systolic Arterial Pressure of 90 mm Hg or Higher. Archives of Internal Medicine. 2005;165(15):1777-81.
13. Kucher N, Rossi E, Rosa MD, Goldhaber SZ. Massive Pulmonary Embolism. 2006;113(4):577-82.
14. Zamorano J-L, Members ATF, Guidelines ECfP, Guidelines ECfP, Guidelines ECfP, Guidelines ECfP, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). European Heart Journal. 2008;29(18):2276-315.
15. Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser KD, et al. Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism: Results of a Multicenter Registry. Journal of the American College of Cardiology. 1997;30(5):1165-71.
16. Masotti L, Righini M, Vuilleumier N, Antonelli F, Landini G, Cappelli R, et al. Prognostic stratification of acute pulmonary embolism: focus on clinical aspects, imaging, and biomarkers. Vascular health and risk management. 2009;5(4):567-75.
17. Torbicki A, Linhart A, Spyropoulos AC, Vonk Noordegraaf A, Perrier A, Hoes A, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)Endorsed by the European Respiratory Society (ERS). European Heart Journal. 2014;35(43):3033-69k.
18. Riedel M. Acute pulmonary embolism 1: pathophysiology, clinical presentation, and diagnosis. Heart. 2001;85(2):229.

19. Miniati M, Cenci C, Monti S, Poli D. Clinical presentation of acute pulmonary embolism: survey of 800 cases. PloS one. 2012;7(2):e30891-e.
20. Stein PD, Terrin ML, Hales CA, Palevsky HI, Saltzman HA, Thompson BT, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest. 1991;100(3):598-603.
21. Todd K, Simpson CS, Redfearn DP, Abdollah H, Baranchuk A. ECG for the diagnosis of pulmonary embolism when conventional imaging cannot be utilized: a case report and review of the literature. Indian pacing and electrophysiology journal. 2009;9(5):268-75.
22. Kearon C. Diagnosis of pulmonary embolism. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2003;168(2):183-94.
23. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Annals of internal medicine. 2001;135(2):98-107.
24. Welfare TSNBoHa. Socialstyrelsens riktlinjer

för vård av blodpropp/venös

tromboembolism 2004. 2004.
25. Kurzyna M, Torbicki A, Pruszczyk P, Burakowska B, Fijalkowska A, Kober J, et al. Disturbed right ventricular ejection pattern as a new Doppler echocardiographic sign of acute pulmonary embolism. Am J Cardiol. 2002;90(5):507-11.
26. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al. Multidetector Computed Tomography for Acute Pulmonary Embolism. New England Journal of Medicine. 2006;354(22):2317-27.
27. Stein PD, Athanasoulis C, Alavi A, Greenspan RH, Hales CA, Saltzman HA, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation. 1992;85(2):462-8.
28. Riedel M. Acute pulmonary embolism 1: pathophysiology, clinical presentation, and diagnosis. 2001;85(2):229-40.
29. Esmon CT. Basic mechanisms and pathogenesis of venous thrombosis. Blood reviews. 2009;23(5):225-9.
30. Turpie AGG, Chin BSP, Lip GYH. Venous thromboembolism: pathophysiology, clinical features, and prevention. BMJ (Clinical research ed). 2002;325(7369):887-90.
31. Cushman M. Epidemiology and risk factors for venous thrombosis. Seminars in hematology. 2007;44(2):62-9.
32. Moheimani F, Jackson DE. Venous thromboembolism: classification, risk factors, diagnosis, and management. ISRN hematology. 2011;2011:124610-.
33. van der Meer RW, Pattynama PM, van Strijen MJ, van den Berg-Huijsmans AA, Hartmann IJ, Putter H, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. Radiology. 2005;235(3):798-803.
34. Araoz PA, Gotway MB, Trowbridge RL, Bailey RA, Auerbach AD, Reddy GP, et al. Helical CT pulmonary angiography predictors of in-hospital morbidity and mortality in patients with acute pulmonary embolism. Journal of thoracic imaging. 2003;18(4):207-16.
35. Bazeed MF, Saad A, Sultan A, Ghanem MA, Khalil DM. Prediction of pulmonary embolism outcome and severity by computed tomography. 2010;51(3):271-6.
36. Ghaye B, Ghuysen A, Willems V, Lambermont B, Gerard P, D'Orio V, et al. Severe pulmonary embolism:pulmonary artery clot load scores and cardiovascular parameters as predictors of mortality. Radiology. 2006;239(3):884-91.
37. Becattini C, Agnelli G, Germini F, Vedovati MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. 2014;43(6):1678-90.
38. Meinel FG, Nance JW, Schoepf UJ, Hoffmann VS, Thierfelder KM, Costello P, et al. Predictive Value of Computed Tomography in Acute Pulmonary Embolism: Systematic Review and Meta-analysis. The American Journal of Medicine. 2015;128(7):747-59.e2.

39. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed Therapy for the Treatment of Massive Pulmonary Embolism: Systematic Review and Meta-analysis of Modern Techniques. Journal of Vascular and Interventional Radiology. 2009;20(11):1431-40.
40. Avgerinos ED, Saadeddin Z, Abou Ali AN, Fish L, Toma C, Chaer M, et al. A meta-analysis of outcomes of catheter-directed thrombolysis for high- and intermediate-risk pulmonary embolism. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2018;6(4):530-40.
41. Goldhaber SZ. Advanced treatment strategies for acute pulmonary embolism, including thrombolysis and embolectomy. Journal of thrombosis and haemostasis : JTH. 2009;7 Suppl 1:322-7.
42. Leacche M, Unic D, Goldhaber SZ, Rawn JD, Aranki SF, Couper GS, et al. Modern surgical treatment of massive pulmonary embolism: Results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. The Journal of Thoracic and Cardiovascular Surgery. 2005;129(5):1018-23.
43. Al-Bawardy R, Rosenfield K, Borges J, Young MN, Albaghdadi M, Rosovsky R, et al. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a case series and review of the literature. Perfusion. 2019;34(1):22-8.
44. Engelberger Rolf P, Kucher N. Catheter-Based Reperfusion Treatment of Pulmonary Embolism. Circulation. 2011;124(19):2139-44.
45. Margheri M, Vittori G, Vecchio S, Chechi T, Falchetti E, Spaziani G, et al. Early and Long-Term Clinical Results of AngioJet Rheolytic Thrombectomy in Patients With Acute Pulmonary Embolism. The American Journal of Cardiology. 2008;101(2):252-8.
46. Siablis D, Karnabatidis D, Katsanos K, Kagadis GC, Zabakis P, Hahalis G. AngioJet Rheolytic Thrombectomy versus Local Intrapulmonary Thrombolysis in Massive Pulmonary Embolism: A Retrospective Data Analysis. Journal of Endovascular Therapy. 2005;12(2):206-14.
47. Pelliccia F, Schiariti M, Terzano C, Keylani AM, D'Agostino DC, Speziale G, et al. Treatment of acute pulmonary embolism: update on newer pharmacologic and interventional strategies. BioMed research international. 2014;2014:410341-.
48. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis Compared With Heparin for the Initial Treatment of Pulmonary Embolism. 2004;110(6):744-9.
49. Stein PD, Matta F. Thrombolytic Therapy in Unstable Patients with Acute Pulmonary Embolism: Saves Lives but Underused. The American Journal of Medicine. 2012;125(5):465-70.
50. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: A Meta-analysisThrombolysis for Pulmonary EmbolismThrombolysis for Pulmonary Embolism. JAMA. 2014;311(23):2414-21.
51. Zarghouni M, Charles HW, Maldonado TS, Deipolyi AR. Catheter-directed interventions for pulmonary embolism. Cardiovascular diagnosis and therapy. 2016;6(6):651-61.
52. Tu T, Toma C, Tapson VF, Adams C, Jaber WA, Silver M, et al. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism. The FLARE Study. 2019;12(9):859-69.
53. Fasullo S, Scalzo S, Maringhini G, Ganci F, Cannizzaro S, Terrazzino G, et al. Six-Month Echocardiographic Study in Patients With Submassive Pulmonary Embolism and Right Ventricle Dysfunction: Comparison of Thrombolysis With Heparin. The American Journal of the Medical Sciences. 2011;341(1):33-9.
54. Sharma G, Folland ED, McIntyre KM, Sasahara AA. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. Vascular Medicine. 2000;5(2):91-5.