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The risk of pulmonary embolism in the context of various clinical situations and management in psychiatric patients

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Summary

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are components of venous thromboembolism (VTE), being the third most common cardiovascular disease. PE is one of the most common life-threatening cardiovascular disorders, which is associated with a mortality of 30% when managed incorrectly. Patients with mental disorders are at higher risk of thromboembolism as compared to the general population and PE is commonly noted in this group. This mainly results from additional thromboembolic risk factors associated with symptoms and treatment of mental disorders. The scores recommended to estimate the VTE risk do not include factors typical of this group of patients.

This article discusses how components of Virchow's triad are activated by symptoms of mental disorders, i.e. psychosis, anxiety, depression and catatonia. The current state of knowledge on the thromboembolic risk associated with coercive measures that involve physical restraint of four limbs is presented. Current data on the thrombotic potential of antipsychotics, antidepressants and electroconvulsive therapy are summarised. Recommendations for the prevention of PE in patients with mental disorders are discussed.

Key words: pulmonary embolism, venous thromboembolism, psychiatry

Introduction

Pulmonary embolism (PE) is a blockage of an artery in the lungs or sections of its branches by an embolic material, being a thrombus originating in 90% of cases from deep veins of lower limbs. PE and deep vein thrombosis (DVT) are components of venous thromboembolism (VTE), being the third most common cardiovascular disease following myocardial infarction and stroke. The annual incidence of PE is 39-115 cases per 100,000 people [1]. Acute PE is one of the most common life-threatening cardiovascular disorders, which is associated with a mortality of 30% when managed incorrectly [2]. VTE and its sequelae are the most common causes of potentially preventable hospital deaths [3].

Patients with mental disorders are at higher risk of VTE as compared to the general population and PE is commonly noted in this group [4]. One study showed that patients diagnosed with a mental disorder suffer from out-of-hospital sudden cardiac arrest (SCA) associated with PE nine times more often than patients without such a diagnosis [5]. Ishida et al. [6] also investigated the percentage of concomitant mental disorders in two groups of patients: with PE and with ST-segment elevation myocardial infarction (STEMI). They found the percentage of patients with mental disorders to be significantly higher among patients with PE than among patients with STEMI. Nevertheless, it seems that less attention is paid to PE as a possible cause of death in this group of patients in clinical practice. Psychiatric patients often have additional thromboembolic risk factors that are not included in the VTE risk scores and are often skipped in studies on this disorder.

1. Pathogenesis

Pathogenesis of VTE is based on three categories of factors described by Rudolf Virchow that are thought to contribute to its development. These include: injury of endothelium in blood vessels, changes in blood composition leading to excessive coagulation and slower blood flow.

Over 90% of PE cases are caused by an embolic material originating from the deep veins of the lower limbs. Thrombi located in these veins detach from the vessel wall and reach pulmonary circulation with blood. Furthermore, simultaneous detachment of a large thrombi may cause massive embolism that will obstruct blood flow through the pulmonary circulation. If this is the case, PE manifests as SCA in the first place. In other cases, severity of symptoms is associated with the amount of embolic material and the individual cardiovascular reserve.

2. Clinical picture

PE is asymptomatic and is detected incidentally during other examinations or autopsy in approximately 50% of patients. The symptoms may also be non-specific and suggest many other disorders. Dyspnoea, chest pain, cough, presyncope/syncope and haemoptysis are the most common symptoms of PE. Over half of patients present with tachypnoea, tachycardia and decreased arterial blood oxygen saturation upon physical examination. DVT symptoms are observed in 1/3 patients with PE. These include: swelling of the lower leg, pain on pressure in the calf, increased warmth in the limb, dilatation of superficial veins which persists when limb is elevated, subfebrile temperature/fever [2, 7].

3. Thromboembolic risk factors in psychiatry

3.1. Symptoms of mental disorders

Psychosis, even left untreated, is associated with increased procoagulant activity. This is probably due to increased adrenaline secretion, which intensifies coagulation mechanisms. This phenomenon is also reflected in laboratory tests. A statistically significant increase in the following parameters associated with coagulation is noted in patients with acute psychosis: D-dimers, P-selectin, expression of GPIIb/IIIa receptors [8]. Additionally, anti-cardiolipin antibodies and lupus anticoagulant were found to be more frequent in patients with psychotic disorders as compared to the control group. Both these compounds are examples of the so-called antiphospholipid antibodies (APLA) and are risk factors for venous thromboembolic complications and arterial thrombosis. Initiation of antipsychotic treatment resulted in an increased number of patients who developed APLA [9]. Emotional stress and anxiety, noted in the course of many mental disorders, increase amounts of cortisol and catecholamines secreted that damage vascular endothelium, which also results in excessive activation of the coagulation system [10, 11].

An increased concentration of homocysteine is another discussed risk factor for VTE, as this amino acid contributes to development of thrombi by damaging the vascular endothelium and changing blood composition [12]. Hyperhomocysteinaemia has been observed in patients with depression and dementia [13, 14].

3.2. Risk in relation to psychiatric diagnosis

The risk of VTE in relation to several psychiatric diagnoses has also been evaluated. A meta-analysis of the risk of VTE in patients with mental disorders was published in 2020. It combines the results of studies published between 1998 and 2019. The results show that the risk of VTE in patients with mental disorders is higher than in the general population and is 1.29-2.2, 1.22-2.14, 1.29 and 1.14-1.49 times higher in patients with psychotic disorders, bipolar disorder, depressive episode and anxiety disorders, respectively [15].

Undoubtedly, the risk of concomitant somatic disorders, including PE, is indirectly increased in patients with mental disorders due to bad habits, such as: smoking, low physical activity, and poor diet.

3.3. Catatonia

Catatonia observed together with mental disorders is associated with an increased risk of somatic complications, including PE, being a frequent cause of death in this group of patients [16]. Stupor and refusal to eat and drink in patients with catatonic syndrome result in prolonged immobility and risk of dehydration, leading to slowed blood flow and hypercoagulability. Psychosis and anxiety, often manifesting during an

underlying disease, may in turn increase coagulation and damage endothelium due to increased secretion of catecholamines and cortisol [10, 11]. These are the components of Virchow's triad, which contribute to VTE.

A literature review discussing 20 case reports of deaths due to PE confirmed by autopsy was published in 1995. All cases included patients with schizophrenia presenting with catatonia for over two weeks. The course of PE was usually asymptomatic. No risk factors for PE had been identified before. In addition, two new cases of sudden death in young women diagnosed with catatonia were presented [17].

A retrospective study analysed medical records of patients who died from 2002 to 2016 at mental health units in Kentucky. Six of 96 deaths were reported in patients with catatonic stupor. Death was sudden in all of them and autopsy confirmed PE. The study additionally analysed how many of the deceased patients would have been saved after modification of treatment, showing 19 such cases. These included all 6 patients with catatonia, which is why it may be concluded that PE in this group of patients is the most common cause of preventable death [18].

D-dimer was tested in patients with suspected symptomatic VTE or at risk of asymptomatic VTE during a study conducted at a psychiatric inpatient hospital in Japan. If D-dimer was above 1 μg/mL, contrast-enhanced CT was performed. The results in catatonic and non-catatonic patients were then compared. The second group additionally consisted of restrained and unrestrained patients. These subgroups were also compared. During the 8-year follow-up, VTE was diagnosed in 2.3% of hospitalised patients, almost all (97.4%) of which were asymptomatic. PE was confirmed in as many as 76.9% patients with VTE. VTE was observed in 61.1% of catatonic patients, 4.1% of non-catatonic restrained patients and in 1.2% non-catatonic unrestrained patients. Anticoagulant therapy was successful in all patients with VTE. This study clearly indicates that the risk of PE is increased in patients hospitalised at mental health units, particularly in patients with symptoms of catatonia [4].

3.4. Coercive measures

The use of coercive measures, such as physical restraint of four limbs, is a factor typical of hospitalisations at mental health units that may increase the risk of thromboembolic complications. Few cases have been reported in the literature. Dickson and Pollanen [19] described three patients who died suddenly when they were restrained for 3-5 days. They had no other thromboembolic risk factors. Autopsy confirmed PE. Post-mortem genetic testing for factor V Leiden and prothrombin mutations was performed and the results were negative [20]. In contrast, authors from Italy presented the case of a 34-year-old man with schizophrenia. The patient had no risk factors for VTE. He was restrained for 6 days because of aggressive behaviour. His condition suddenly deteriorated after this time. He was diagnosed with PE. Despite fibrinolysis and treatment with unfractionated heparin, the patient died [20].

Case reports of patients who died from 2010 to 2014 at a mental health unit in Hong Kong were analysed. PE confirmed by autopsy was the cause of death in 4 of 34 deceased patients. Long-term antipsychotic treatment was reported in 2 of 4 patients. Physical restraint of four limbs was applied in all 4 patients shortly before collapse and subsequent SCA [21]. A relationship between duration of physical restraint and the risk of PE was assessed. A study published in 2021 found that a higher total number of days of physical restraint was associated with a significantly higher risk of pulmonary embolism. The authors of the article suspect that it takes place because blood flow is slowed down in retrained lower limbs, which, in addition with limited water intake, leads to hypercoagulability [22].

Contrary to the above, Skowronek et al. [23] claim that correctly performed physical restraint of patients with mental disorders does not shut down the muscle pump, so it should not lead to stasis [24]. Authors of another study [24] suggest, however, that physical restraint may increase the risk of thromboembolism by activating another component of Virchow's triad. They explain that restrained patients are often agitated and damage their vessel walls while struggling with belts. In the proposed algorithm for the primary prevention of VTE in patients hospitalised at mental health units physical restraint lasting ≥ 8 h is considered a risk factor [25].

3.5. Antipsychotics

It has been known for many years that antipsychotics (APs) are associated with an increased risk of thrombosis. The first references to the effects of these medications on VTE were made shortly after introduction of chlorpromazine. A review article discussing 49 such cases was published in 1965 [26]. Further confirming reports were published in the following years. As a consequence, information on the risk of VTE was provided in the summary of product characteristics of any marketed AP.

An increased risk of thromboembolic complications has been shown for both generations of APs, with the risk being higher in the case of second-generation (atypical) APs as compared to first-generation (typical) APs. As far as typical APs are concerned, less potent medications are more likely to cause VTE than more potent ones. Combination treatment with the first- and second-generation APs is associated with thromboembolic risk comparable to the risk of treatment with a single second-generation AP. On the basis of these data, the authors suggest that in the case of the need for immediate use of APs the single use of first-generation APs is the safest therapeutic strategy, rather than single use of second-generation APs or combination treatment [27]. The highest risk of VTE was found for clozapine. Other APs most commonly referred to in terms of the risk of thromboembolic complications include olanzapine and risperidone, along with sertindole, quetiapine and zuclopenthixol [28]. Thromboembolic risk associated with APs increased with the dose administered and with polytherapy [29]. Current studies do not specify which AP is

associated with the lowest risk of VTE. Aripiprazole seems to be a safer alternative in patients at risk [30].

Many hypotheses were formulated on the development of thrombosis during treatment with APs. Most likely mechanisms leading to this complication differ among each group of medications due to the different mechanisms of their antipsychotic action. The first-generation APs may cause thrombosis as they increase platelet aggregation and antiphospholipid antibody levels. They also have a strong sedative effect, which with reduced physical activity slows down blood flow [31]. The second-generation APs indirectly increase the risk of VTE as they are associated with adverse effects, such as symptoms of metabolic syndrome and weight gain. They may also cause thrombosis by increasing platelet aggregation. Such effects have been described for clozapine [32]. Hyperprolactinaemia is a common adverse effect of APs. Prolactin is a potent co-activator of adenosine diphosphate (ADP)-dependent platelet aggregation; therefore, its increased levels promote venous and arterial thrombosis [33].

Studies show that the risk of thromboembolic complications is highest at the beginning of antipsychotic treatment (for the first 3 months) and decreases over time [34]. A meta-analysis published in 2021 showed that the risk of PE and VTE in younger patients (aged <60) treated with APs is three times higher as compared to the elderly (aged >60) [27]. This may result from lower doses of APs used in the elderly and from the fact that most disorders that require antipsychotics develop in younger patients and, as mentioned above, thromboembolic complications were mostly observed at the beginning of treatment.

Some data suggest that injectable (short-acting or depot) medications may be associated with higher risk of VTE than oral medications [34].

3.6. Antidepressants

The results of a large prospective study conducted in the UK under the title "The Million Women Study" were published in 2017. Its objective was, among others, to determine whether an increased risk of VTE in female patients with depression is associated with the disorder itself or results from its treatment. Female study subjects were divided into four groups:

(1) "no treatment/no drugs" – control group: women who reported not being treated for depression and no use of antidepressants or other psychotropic drugs for most of the last 4 weeks;
(2) "treatment/no drugs" – women who reported being treated for depression and no use of antidepressants or other psychotropic drugs for most of the last 4 weeks;
(3) "antidepressants" – women who reported use of antidepressants for most of the last 4 weeks;
(4) "other psychotropics" – women who reported use of other psychotropic drugs for most of the last 4 weeks.

An increased risk of VTE was found in groups 3 and 4 as compared to group 1 (control group) and group 2. The risk of VTE in women who reported being treated for depression but no use of antidepressants or other psychotropic drugs (group 2) was slightly higher. It may be concluded that treatment with antidepressants or psychotropic drugs that belong to other groups predisposes to the development of thrombosis more than depression itself. The risk associated with use of antidepressants from specific groups was also investigated. Women who reported being treated with antidepressants were divided into three groups: those treated with tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and other antidepressants. No significant differences between these groups were demonstrated [35].

On the other hand, a meta-analysis published in 2019 showed no association between SSRIs and the risk of VTE. It was concluded that TCAs may be associated with an increased risk of VTE, but the quality of evidence was very low [36].

3.7. Electroconvulsive therapy

Single case reports suggest an association between electroconvulsive treatments (ECTs) and PE. It is likely that, despite administration of succinylcholine, a generalised seizure during an ECT induces muscle contractions that may displace a peripheral clot [37]. A case who developed PE during a series of ECTs was reported in 2019. The patient presented with multiple thromboembolic risk factors (obesity, reduced physical activity, depression and use of antidepressants) but was not eligible for thromboprophylaxis according to current algorithms. He survived because of an immediate intervention and ECTs were continued with good results and without further complications after his condition had been stabilised and anticoagulant therapy had been initiated [39].

Conditions that require ECTs, such as catatonia, are undoubtedly associated with an increased risk of thromboembolic complications. Particular attention should be paid to symptoms of DVT in these patients. If DVT is diagnosed in a patient qualified for ECTs, it is important to determine the location of thrombosis. As compared to distal thrombosis, proximal thrombosis is associated with a significantly higher risk of massive PE, and sudden cardiac arrest may be its first symptom. It was determined that ECTs can be safely performed in patients with distal DVT treated with anticoagulants; anticoagulation should be continued in patients with proximal DVT and ECTs can be initiated only after thrombosis has resolved [39]. A case series published by Inagawa et al. [40] also confirms these observations.

4. Prevention

There is no validated score to assess the risk of VTE taking into account factors specific to patients with mental disorders. An algorithm for the primary prevention of VTE in patients hospitalised at mental health units [25] and in elderly patients with

mental disorders was suggested [41]. QThrombosis®-2018 [42] is a risk calculator that takes into account the use of antipsychotics. The tool is available online at http://qthrombosis.org.

There are no references to patients with mental disorders in Polish guidelines concerning VTE. Recommendations for patients treated conservatively should be followed with the Padua Prediction Score used to assess the risk of VTE. The scale is used to assess 11 risk factors for VTE, each assigned a score from 1 to 3. A total score ≥4 indicates high risk of VTE and is an indication for thromboprophylaxis [43]. Guidelines for thromboprophylaxis published by the National Institute for Health and Care Excellence (NICE) include patients with mental disorders, but recommend risk assessment identical to that of internal medicine patients [7]. The assessment of the risk of thromboembolism should be made at the first examination of the patient, and then each time the patient's condition changes or after obtaining additional information that may be of importance in the risk calculation.

Primary prevention of VTE may be divided into mechanical and pharmacological. Mechanical methods (compression stockings and intermittent pneumatic compression devices) are indicated in patients at high risk of VTE and bleeding [43]. In other cases, pharmacological prevention is indicated. NICE recommends low-molecular-weight heparin (LMWH) in patients with mental disorders or fondaparinux if LMWH is contraindicated [7]. An important preventive measure is also to avoid dehydration, initiate physical rehabilitation and encourage patients to undertake physical activity.

Conclusions

If PE is suspected in a psychiatric patient, the clinical likelihood should be assessed using prediction rules, e.g. the Wells rule. Details of the diagnostic process are included in the 2019 guidelines of the European Society of Cardiology on the diagnosis and management of acute pulmonary embolism [44].

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